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NEWS 2	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
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NEWS 5	NOV 19	WPIX enhanced with XML display format
NEWS 6	NOV 30	ICSD reloaded with enhancements
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NEWS 9	DEC 17	USPATOLD added to additional database clusters
NEWS 10	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS 11	DEC 17	DGENE now includes more than 10 million sequences
NEWS 12	DEC 17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS 13	DEC 17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
NEWS 14	DEC 17	CA/CAplus enhanced with new custom IPC display formats
NEWS 15	DEC 17	STN Viewer enhanced with full-text patent content from USPATOLD
NEWS 16	JAN 02	STN pricing information for 2008 now available
NEWS 17	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS 18	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS 19	JAN 28	MARPAT searching enhanced
NEWS 20	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS 21	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS 22	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
NEWS 23	FEB 08	STN Express, Version 8.3, now available
NEWS 24	FEB 20	PCI now available as a replacement to DPCI
NEWS 25	FEB 25	IFIREF reloaded with enhancements
NEWS 26	FEB 25	IMSPRODUCT reloaded with enhancements
NEWS 27	FEB 29	WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification

NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
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L1 0 EMBASE BIOSIS MEDLINE CAPLUS

=> s src and (blood pressure or hypertension or hypotension or normotensive)
1 FILES SEARCHED...
L2 570 SRC AND (BLOOD PRESSURE OR HYPERTENSION OR HYPOTENSION OR NORMOTENSIVE)

=> s l2 and inhibitor
L3 286 L2 AND INHIBITOR

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 159 DUP REM L3 (127 DUPLICATES REMOVED)

=> s l4 and py<=2003
L5 66 L4 AND PY<=2003

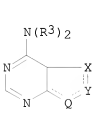
=> d l5 ibib abs 1-66

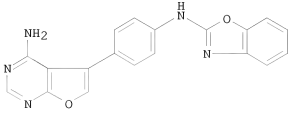
L5 ANSWER 1 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:950055 CAPLUS
DOCUMENT NUMBER: 140:5065
TITLE: Preparation of pyrazolopyrimidine and furopyrimidine protein kinase inhibitors and their therapeutic use
INVENTOR(S): Hirst, Gavin C.; Arnold, Lee D.; Burchat, Andrew; Wishart, Neil; Calderwood, David; Wada, Carol K.; Michaelides, Michael R.; Ji, Zhiqin; Muckey, Melanie
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 44 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003225098	A1	20031204	US 2003-394965	20030321 <--
PRIORITY APPLN. INFO.:			US 2002-366422P P	20020321

OTHER SOURCE(S): MARPAT 140:5065
GI


I


II

AB Title compds. I [X = CR1, NR; Y = O, alkyl, N; Q = N, NR2, O; R3 = H, OH, alkyl, alkoxy; R = H, alkyl, arylalkyl, aryl; R1 = pyrimidinyl, etc.; R2 = piperidinyl, etc.] are prepared For instance, 5-(4-aminophenyl)furo[2,3-d]pyrimidin-4-amine (preparation given) is treated with 1,1-thiocarbonyldiimidazole/pyridine at 0° followed by 2-aminophenol/EDCI and heated to 55° for 8 h to give II. I are useful as kinase inhibitors and are useful in the treatment of hyperproliferative disorders, ulcers, etc.

L5 ANSWER 2 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:777596 CAPLUS
DOCUMENT NUMBER: 139:272922
TITLE: Pyrazolopyrimidine and furopyrimidine protein kinase inhibitors and their therapeutic use
INVENTOR(S): Hirst, Gavin C.; Arnold, Lee D.; Burchat, Andrew; Wishart, Neil; Calderwood, David; Wada, Carol K.; Michaelides, Michael R.; Ji, Zhiqin; Muckey, Melanie
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080064	A1	20031002	WO 2003-US8950	20030321 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003199525	A1	20031023	US 2002-103098	20020321	<--
CA 2477651	A1	20031002	CA 2003-2477651	20030321	<--
AU 2003222055	A1	20031008	AU 2003-222055	20030321	<--
EP 1496910	A1	20050119	EP 2003-718039	20030321	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2005530713	T	20051013	JP 2003-577890	20030321	
MX 2004PA09140	A	20041126	MX 2004-PA9140	20040921	
PRIORITY APPLN. INFO.:			US 2002-103098	A 20020321	
			WO 2003-US8950	W 20030321	

OTHER SOURCE(S): MARPAT 139:272922

AB The present application is directed to pyrazolopyrimidine and furopyrimidine analogs which are useful as protein kinase inhibitors. These compds. may be used in treatment of hyperproliferative disorders, ulcers, etc.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:532691 CAPLUS

DOCUMENT NUMBER: 139:95435

TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands

INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus

PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.

SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2003055914	A2	20030710	WO 2002-DK900	20021220	<--
WO 2003055914	A3	20031023			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2002358469	A1	20030715	AU 2002-358469	20021220	<--
PRIORITY APPLN. INFO.:			DK 2001-1944	A 20011221	
			DK 2002-113	A 20020122	
			DK 2002-1043	A 20020703	
			US 2002-394122P	P 20020703	
			WO 2002-DK900	W 20021220	

AB A drug discovery method is provided for selecting a compound selected from the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in

a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L5 ANSWER 4 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:282027 CAPLUS
DOCUMENT NUMBER: 138:298122
TITLE: Identification of human mineralocorticoid receptor (MCR)-interacting proteins using the yeast two-hybrid assay, cloning and sequencing of the MCR-interacting protein PN19395, and therapeutic and diagnostic applications
INVENTOR(S): Cimbora, Daniel M.; Heichman, Karen; Bartel, Paul L.
PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 29 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003068630	A1	20030410	US 2002-105959	20020321 <--
PRIORITY APPLN. INFO.:			US 2001-278428P	P 20010326

AB The present invention relates to the discovery of novel ligand-dependent protein-protein interactions that are involved in mammalian physiol. pathways, including physiol. disorders or diseases. The interacting proteins for mineralocorticoid receptor (MCR) are identified using the yeast two-hybrid method and searching a human total brain library. These ligand-dependent MCR interactors are: the pro-inflammatory transcription factor NF-κB1 (p50); the nuclear hormone receptor coactivator NCOA1 (SRC-1); the hormone-regulated transcription factor FKHR, ASC-2, a general coactivator of nuclear hormone receptors; the nuclear hormone receptor coactivator PGC-1; the transcription factor TIF1A; phosphoglycerate kinase 1 (PGK1); and the novel protein PN19395. The

nucleotide sequence and the encoded amino acid sequence of the human protein PN19395 are disclosed. Examples of physiol. disorders and diseases include non-insulin dependent diabetes mellitus (NIDDM), neurodegenerative disorders, such as Alzheimer's Disease (AD), and the like. Thus, the present invention is directed to complexes of these proteins and/or their fragments, antibodies to the complexes, diagnosis of physiol. generative disorders (including diagnosis of a predisposition to and diagnosis of the existence of the disorder), drug screening for agents which modulate the interaction of proteins described herein, and identification of addnl. proteins in the pathway common to the proteins described herein.

L5 ANSWER 5 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:937303 CAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A	20021210	JP 2002-69354		20020313 <--
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L5 ANSWER 6 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:806176 CAPLUS
DOCUMENT NUMBER: 138:83734
TITLE: Tyrosine kinases regulate intracellular calcium during α2-adrenergic contraction in rat aorta
AUTHOR(S): Carter, Rebecca W.; Kanagy, Nancy L.
CORPORATE SOURCE: Department of Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, NM, 87131-5218, USA
SOURCE: American Journal of Physiology (2002), 283(4, Pt. 2), H1673-H1680
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have demonstrated enhanced contractile sensitivity to the α2-adrenoreceptor (α2-AR) agonist UK-14304 in arteries from rats made hypertensive with chronic nitric oxide synthase (NOS) inhibition (LHR) compared with arteries from normotensive rats (NR); addnl., this contraction requires Ca2+ entry. The authors hypothesized that tyrosine kinases augment α2-AR contraction in LHR arteries by increasing Ca2+. The tyrosine kinase inhibitor tyrphostin 23 significantly attenuated UK-14304 contraction of denuded thoracic aortic rings from NR and LHR. However, tyrphostin 23 did not alter UK-14304 contraction in ionomycin-permeabilized aorta, which indicates that tyrosine kinases regulate intracellular Ca2+ concentration The Src family inhibitor PP1 and the epidermal growth factor receptor kinase inhibitor AG-1478 did not alter α2-AR contraction, whereas the mitogen-activated protein kinase extracellular signal-regulated kinase kinase inhibitor PD-98059 attenuated the contraction. Contraction to CaCl2 in ionomycin-permeabilized LHR rings was greater than in NR rings. UK-14304 augmented CaCl2 contraction in ionomycin-permeabilized rings from both groups but to a greater extent in LHR aorta. Together, these data suggest that α2-AR stimulates contraction via two pathways. One, which is enhanced with NOS inhibition hypertension, activates Ca2+ sensitivity and is independent of tyrosine kinases. The other is tyrosine kinase dependent and regulates intracellular Ca2+ concentration

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:760113 CAPLUS

DOCUMENT NUMBER: 138:51278

TITLE: Roles of tyrosine kinase-, 1-phosphatidylinositol 3-kinase-, and mitogen-activated protein kinase-signaling pathways in ethanol-induced contractions of rat aortic smooth muscle possible relation to alcohol-induced hypertension

AUTHOR(S): Yang, Zhi-wei; Wang, Jun; Zheng, Tao; Altura, Bella T.; Altura, Burton M.

CORPORATE SOURCE: State University of New York, Department of Physiology and Pharmacology, Health Science Center at Brooklyn, Brooklyn, NY, 11203, USA

SOURCE: Alcohol (New York, NY, United States) (2002), 28(1), 17-28
CODEN: ALCOEX; ISSN: 0741-8329

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insights into the relations between and among ethanol-induced contractions in rat aorta, tyrosine kinases (including src family of cytoplasmic tyrosine kinases), 1-phosphatidylinositol 3-kinases (PI-3Ks), mitogen-activated protein kinases (MAPKs), and regulation of intracellular free Ca2+ ([Ca2+]i) were investigated in the present study. Ethanol-induced concentration-dependent contractions in isolated rat aortic rings were attenuated greatly by pretreatment of the arteries with low concns. of an antagonist of protein tyrosine kinases (genistein), an src homol. domain 2 (SH2) inhibitor peptide, a highly specific antagonist of p38 MAPK (SB-203580), a potent, selective antagonist of two specific MAPK kinases-MEK1/MEK2 (U0126)-and a selective antagonist of mitogen-activated protein kinase kinase (MAPKK) (PD-98059), as well as by treatment with wortmannin or LY-294002 (both are selective antagonists of PI-3Ks). Inhibitory concentration 50 (IC50) levels obtained for these seven antagonists were consistent with reported inhibition constant (Ki) values

for these tyrosine kinase, MAPK, and MAPKK antagonists. Ethanol-induced transient and sustained increases in [Ca2+]i in primary single smooth muscle cells from rat aorta were markedly attenuated in the presence of genistein, an SH2 domain inhibitor peptide, SB-203580, U0126, PD-98059, wortmannin, and LY-294002. A variety of specific antagonists of known endogenously formed vasoconstrictors did not inhibit or attenuate either the ethanol-induced contractions or the elevations of [Ca2+]i. Results of the present study support the suggestion that activation of tyrosine kinases (including the src family of cytoplasmic tyrosine kinases), PI-3Ks, and MAPK seems to play an important role in ethanol-induced contractions and the elevation of [Ca2+]i in smooth muscle cells from rat aorta. These signaling pathways thus may be important in hypertension in human beings associated with chronic alc. consumption.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:362622 CAPLUS
DOCUMENT NUMBER: 136:322855
TITLE: Signal transduction of angiotensin and vascular remodeling in hypertension
AUTHOR(S): Schiffrin, Ernesto L.
CORPORATE SOURCE: Montreal Univ., Can.
SOURCE: Cardiac Practice (2002), 13(2), 235-241 CODEN: CARPEM; ISSN: 0915-874X
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review on (1) relationship between endothelium injury and cardiovascular events, (2) changes in microvessels in hypertension, (3) biosynthetic pathway of angiotensin II (AII), (4) effects of AII on vascular systems, (5) signal transduction of AII, (6) NADH/NADPH oxidase-mediated oxidative stress, (7) Src activation and vascular remodeling by AII, (8) normalization of media to lumen ratio and endothelial functions by ACE inhibitors in patients with hypertension, and (9) prevention of the cardiovascular complications of hypertension by renin-angiotensin system inhibitors.

L5 ANSWER 9 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:161658 CAPLUS
DOCUMENT NUMBER: 136:338676
TITLE: Increased angiotensin II-mediated Src signaling via epidermal growth factor receptor transactivation is associated with decreased C-terminal Src kinase activity in vascular smooth muscle cells from spontaneously hypertensive rats
AUTHOR(S): Touyz, Rhian M.; Wu, Xiao-Hua; He, Gang; Salomon, Steven; Schiffrin, Ernesto L.
CORPORATE SOURCE: Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, Montreal, QC, Can.
SOURCE: Hypertension (2002), 39(2, Pt. 2), 479-485 CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated whether upregulation of Src by Ang II leads to increased extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in vascular smooth muscle cells (VSMCs) from spontaneously

hypertensive rats (SHR) and whether these processes are associated with altered activation of C-terminal Src kinase (Csk), a neg. regulator of Src. Furthermore, the role of epidermal growth factor receptor (EGFR) transactivation by angiotensin II (Ang II) was determined Ang II-mediated c-Src phosphorylation was significantly greater (≈4-fold, P<0.01) in SHR than in Wistar-Kyoto rats (WKY). Ang II increased Csk phosphorylation 2-to 3-fold in WKY but not in SHR. Treatment of the cells with AG1478, a selective EGFR tyrosine kinase inhibitor, decreased Ang Ii-mediated c-Src phosphorylation, particularly in SHR. Phosphorylation of cortactin and Pyk2/focal adhesion kinase, Src-specific substrates, was increased by Ang 11 >3-fold, with significantly greater responses in SHR than in WKY (P<0.05). Ang II-induced ERKI/2 activation was significantly augmented (P<0.05) and sustained in VSMCs from SHR. PP2, a selective Src inhibitor, attenuated these effects and normalized the responses in SHR. Irbesartan, a selective Ang II type 1 receptor blocker, but not PD123319, a selective Ang II type 2 receptor blocker, inhibited Ang II actions. Our results demonstrate that c-Src phosphorylation and Src-dependent ERK1/2 signaling by Ang II are increased in VSMCs from SHR. These processes are associated with blunted Ang II-induced phosphorylation of Csk. EGFR transactivation contributes to Ang II-mediated Src-dependent ERK1/2 signaling. In conclusion, altered regulation of Ang II type 1 receptor-activated c-Src by Csk may be an important upstream modulator of abnormal ERKI/2 signaling in VSMCs from SHR.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:924518 CAPLUS
DOCUMENT NUMBER: 136:129365
TITLE: Synergistic effect of urotensin II with serotonin on vascular smooth muscle cell proliferation
AUTHOR(S): Watanabe, Takuya; Pakala, Rajbabu; Katagiri, Takashi; Benedict, Claude R.
CORPORATE SOURCE: Department of Internal Medicine, Division of Cardiology, University of Texas-Houston Health Science Center, Houston, TX, 77030, USA
SOURCE: Journal of Hypertension (2001), 19(12), 2191-2196
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Urotensin II (U-II), the most potent vasoconstrictor, and serotonin (5-HT) are known to play an important role in pulmonary hypertension. However, little is known about the effect of U-II and its interaction with 5-HT on vascular smooth muscle cell (VSMC) proliferation. In this study the authors assessed the interaction between U-II and 5-HT in inducing VSMC proliferation. Growth-arrested rabbit VSMCs were incubated in serum-free medium with different concns. of U-II and 5-HT. VSMC proliferation was examined by the increase in [3H]thymidine incorporation into DNA and cell number U-II or 5-HT induced [3H]thymidine incorporation in a dose-dependent manner with a maximal effect at a concentration of 50 nM (161%) or 50 μM (205%), resp. When added together, low concns. of U-II (50 nM) and 5-HT (1 μM) interacted synergistically in inducing [3H]thymidine incorporation (382%). These effects on [3H]thymidine incorporation were paralleled by an increase in cell number The G-protein inactivator GDP-β-S (100 μM), protein kinase C (PKC) inhibitor Ro31-8220 (0.1 μM), Src family tyrosine kinase inhibitor PP2 (1 μM), and mitogen-activated protein

kinase (MAPK) kinase inhibitor PD098059 (10 μM) inhibited the mitogenic effects of U-II and 5-HT and also their interaction in inducing [3H]thymidine incorporation. The authors' results suggest that U-II and 5-HT may induce the synergistic interaction in inducing VSMC proliferation via a G-protein-coupled receptor/PKC/Src tyrosine kinase/MAPK pathway, thus contributing to the relatively rapid development of atherosclerosis in hypertensive vascular disease.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:845549 CAPLUS
DOCUMENT NUMBER: 136:80313
TITLE: Src family kinases mediate epithelial Na+ channel inhibition by endothelin
AUTHOR(S): Gilmore, Elaine S.; Stutts, M. Jackson; Milgram, Sharon L.
CORPORATE SOURCE: Department of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA
SOURCE: Journal of Biological Chemistry (2001), 276(45), 42610-42617
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The epithelial Na+ channel (ENaC) is implicated in the pathogenesis of salt-sensitive hypertension. Recent evidence from animal models suggests that the vasoactive peptide, endothelin (ET-1), may be an important neg. regulator of ENaC in vivo. We investigated the signaling pathway involved in endothelin-mediated ENaC inhibition. Expts. were performed in NIH 3T3 cells stably expressing genes for the three (α, β, and γ) ENaC subunits. In whole cell patch clamp expts., we found that ET-1 treatment induced a dose-dependent decrease in amiloride-sensitive currents. Using receptor-specific antagonists, we determined that the effects of ET-1 were attributed to activation of the ETB receptor. Moreover, the inhibitory effect of ET-1 on ENaC could be completely blocked when cells were pretreated with the selective Src family kinase inhibitor, PP2. Further studies revealed that basal Src family kinase activity strongly regulates ENaC whole cell currents and single channel gating. These results suggest that Src family kinases lie in a signaling pathway activated by ET-1 and are components of a novel neg. regulatory cascade resulting in ENaC inhibition.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:566374 CAPLUS
DOCUMENT NUMBER: 135:271110
TITLE: Src is an important mediator of extracellular signal-regulated kinase 1/2-dependent growth signaling by angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients
AUTHOR(S): Touyz, Rhian M.; He, Gang; Wu, Xiao-Hua; Park, Jeong Bae; El Mabrouk, Mohammed; Schiffrin, Ernesto L.
CORPORATE SOURCE: Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Montreal, QC, 112W 1R7, Can.
SOURCE: Hypertension (2001), 38(1), 56-64

CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of c-Src in growth signaling by angiotensin (Ang) II was investigated in vascular smooth muscle cells (VSMCs) from arteries of hypertensive patients. c-Src and extracellular signal-regulated kinase 1/2 (ERK1/2) activity, proto-oncogene expression, activating protein-I (AP-I) DNA-binding activity, and DNA and protein synthesis were studied in Ang II-stimulated VSMCs derived from small peripheral resistance arteries of normotensive subjects (NTs, n=5) and age-matched untreated hypertensive patients (HTs, n= 10). Ang II type I (AT1) and type 2 (AT2) receptor status was also asessed. Ang II dose-dependently increased the synthesis of DNA and protein, with enhanced effects in VSMCs from HTs. PD 098.059, a selective inhibitor of the ERK1/2 pathway, attenuated Ang II-stimulated growth in HTs. The effects of PD 098,059 were greater in HTs than in NTs. In NTs, Ang II transiently increased ERKI/2 phosphorylation, whereas in HTs, Ang II-stimulated actions were augmented and sustained. PP2, a selective Src inhibitor, reduced ERKI/2 activity and normalized ERK1/2 responses in HTs. Ang IL-induced c-Src phosphorylation was 2- to 3-fold greater in HTs than in NTs. In HTs but not NTs. kinase activation was followed by overexpression of c-fos and enhanced AP-DNA-binding activity. PD 098,059 and PP2 attenuated these responses. AT, receptor expression was similar in NTs and HTs. In HT cells transfected with c-fos antisense oligodeoxynucleotide, Ang II-stimulated growth was reduced compared with sense oligodeoxynucleotide. Our findings suggest that augmented Ang II-stimulated VSMC growth is mediated via hyperactivation of c-Src-regulated ERK1/2-dependent pathways, leading to overexpression of c-fos mRNA and enhanced AP-I DNA-binding activity. Because AT1 receptor expression was unaltered in HTs, increased angiogenesis signaling may be a postreceptor phenomenon. These data define a signal transduction pathway whereby Ang II mediates exaggerated growth in VSMCs from HTs.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:563524 CAPLUS
DOCUMENT NUMBER: 135:283524
TITLE: Synergistic effect of urotensin II with mildly oxidized LDL on DNA synthesis in vascular smooth muscle cells
AUTHOR(S): Watanabe, Takuya; Pakala, Rajbabu; Katagiri, Takashi; Benedict, Claude R.
CORPORATE SOURCE: Department of Internal Medicine, University of Texas, Houston, TX, 77030, USA
SOURCE: Circulation (2001), 104(1), 16-18
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The urotensin II (UII) found in coronary atheroma is the most potent vasoconstrictor known to date. Mildly oxidized LDL (moxLDL) contributes to atherogenesis and plaque formation. The authors assessed the effect of UII and its interaction with moxLDL and the oxidative components of moxLDL on vascular smooth muscle cell (VSMC) proliferation. Growth-arrested VSMCs were incubated in serum-free medium with different concns. of LDL, moxLDL, oxLDL, hydrogen peroxide, lysophosphatidylcholine, or 4-hydroxy-2-nonenal, with or without UII. [3H]Thymidine incorporation into DNA was measured as an index of VSMC proliferation. UII stimulated [3H]thymidine incorporation in a dose-dependent manner, with a maximal

effect at a concentration of 50 nmol/L (161%). Low concns. of UII potentiated the mitogenic effect of LDL (108% to 242%), oxLDL (129% to 302%), moxLDL (120% to 337%), hydrogen peroxide (177% to 226%), lysophosphatidylcholine (115% to 332%), and 4-hydroxy-2-nonenal (142% to 299%). The synergistic interaction between UII and moxLDL was partially inhibited by anti-Gq/11α antibody, the epidermal growth factor receptor tyrosine kinase inhibitor erbstatin A (10 μM), and the intracellular free radical scavenger N-acetylcysteine (400 μM) and was completely inhibited by the c-Src tyrosine kinase inhibitor radicicol (10 μM), the protein kinase C (PKC) inhibitor Ro31-8220 (0.1 μM), and the mitogen-activated protein kinase (MAPK) kinase inhibitor PD098059 (10 μM). The authors' results suggest that UII acts synergistically with moxLDL in inducing VSMC proliferation via the c-Src/PKC/MAPK pathway, which may explain the relatively rapid progression of atherosclerosis in patients with hypertension and hypercholesterolemia.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:293997 CAPLUS

DOCUMENT NUMBER: 134:348566

TITLE: Epidermal growth factor receptor transactivation by angiotensin II requires reactive oxygen species in vascular smooth muscle cells

AUTHOR(S): Ushio-Fukai, Masuko; Griendling, Kathy K.; Becker, Peter L.; Hilenski, Lula; Halleran, Sean; Alexander, R. Wayne

CORPORATE SOURCE: Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, 30322, USA

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2001), 21(4), 489-495
CODEN: ATVBFA; ISSN: 1079-5642

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiotensin II (Ang II) is a vasoactive hormone with critical roles in vascular smooth muscle cell growth, an important feature of hypertension and atherosclerosis. Many of these effects are dependent on the production of reactive oxygen species (ROS). Ang II induces phosphorylation of the epidermal growth factor (EGF) receptor (EGF-R), which serves as a scaffold for various signaling mols. Here, we provide novel evidence that ROS are critical mediators of EGF-R transactivation by Ang II. Pretreatment of vascular smooth muscle cells with the antioxidants diphenylene iodonium, Tiron, N-acetylcysteine, and ebselen significantly inhibited (≈ 80% to 90%) tyrosine phosphorylation of the EGF-R by Ang II but not by EGF. Of the 5 autophosphorylation sites on the EGF-R, Ang II mainly phosphorylated Tyr1068 and Tyr1173 in a redox-sensitive manner. The Src family kinase inhibitor PP1, overexpression of kinase-inactive c-Src, or chelation of intracellular Ca2+ attenuated EGF-R transactivation. Although antioxidants had no effects on the Ca2+ mobilization or phosphorylation of Ca2+-dependent tyrosine kinase Pyk2, they inhibited c-Src activation by Ang II, suggesting that c-Src is l signaling mol. that links ROS and EGF-R phosphorylation. Furthermore, Ang II-induced tyrosine phosphorylation of the autophosphorylation site and the SH2 domain of c-Src was redox sensitive. These findings emphasize the importance of ROS in specific Ang II-stimulated growth-related signaling pathways and suggest that redox-sensitive EGF-R transactivation may be a potential target for antioxidant therapy in vascular disease.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:266432 CAPLUS
DOCUMENT NUMBER: 135:44541
TITLE: Differential activation of extracellular signal-regulated protein kinase 1/2 and p38 mitogen activated-protein kinase by AT1 receptors in vascular smooth muscle cells from Wistar-Kyoto rats and spontaneously hypertensive rats
AUTHOR(S): Touyz, Rhian M.; He, Gang; El Mabrouk, Mohammed; Diep, Quy; Mardigyan, Vartan; Schiffrin, Ernesto L.
CORPORATE SOURCE: Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Can.
SOURCE: Journal of Hypertension (2001), 19(3, Pt. 2), 553-559
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objectives The present study investigates effects of angiotensin II on activation of extracellular signal-regulated protein kinase (ERK) 1/2, p38 mitogen activated-protein kinase (p38MAPK) and c-Jun amino terminal kinase (JNK) in vascular smooth muscle cells from spontaneously hypertensive rats (SHR). Methods Vascular smooth muscle cells (VSMC) from mesenteric arteries of Wistar-Kyoto (WKY) rats and SHR were studied. Angiotensin II-induced phosphorylation of ERK1/2, JNK and p38MAPK were assessed by Western blot anal. C-fos mRNA expression by angiotensin II was determined by reverse transcriptase-polymerase chain reaction in the absence and presence of PD98059, selective inhibitor of ERK1/2-dependent pathways and SB202190, selective p38MAPK inhibitor. Results Angiotensin II increased phosphorylation of ERK1/2 and p38MAPK, but not JNK. Responses were significantly increased in SHR compared with WKY. Irbesartan, AT1 receptor antagonist, but not PD123319, AT2 receptor blocker, abolished angiotensin II-induced effects. PP2, selective Src inhibitor, decreased angiotensin II-mediated activation of MAP kinases. Angiotensin II increased c-fos mRNA expression in SHR and had a small stimulatory effect in WKY. These actions were inhibited by PD98059, whereas SB202190 had no effect. Conclusions Angiotensin II-induced activation of vascular ERK1/2 and p38MAPK is increased in SHR. These effects are mediated via AT1 receptors, which activate Src-dependent pathways. Overexpression of c-fos mRNA in SHR is due to ERK1/2-dependent, p38MAPK-independent pathways. Our results suggest that angiotensin II activates numerous MAP kinases in VSMCs and that differential activation of these kinases may be important in altered growth signaling in VSMCs from SHR.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:213530 CAPLUS
DOCUMENT NUMBER: 135:3926
TITLE: Src tyrosine kinases and extracellular signal-regulated 0/kinase 1/2 mitogen-activated protein kinases mediate pressure-induced c-fos expression in cannulated rat mesenteric small arteries
AUTHOR(S): Wesselman, Jos P. M.; Dobrian, Anca D.; Schriver, Suzanne D.; Prewitt, Russell L.
CORPORATE SOURCE: Department of Physiological Sciences, Eastern Virginia Medical School, Norfolk, VA, USA
SOURCE: Hypertension (2001), 37(3), 955-960
CODEN: HPRTDN; ISSN: 0194-911X

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chronic hypertension is associated with remodeling of small arteries. There is evidence that the high pressure itself may cause these structural changes, but the responsible mechanisms are not clearly defined. Previously we showed that pressure-induced c-fos expression in intact cannulated rat mesenteric small arteries was inhibited by genistein, a general tyrosine kinase inhibitor. The purpose of this study was to further unravel the underlying signal transduction mechanisms, and we particularly tested the involvement of src tyrosine kinases and extracellular signal-regulated kinase (ERK). Rat mesenteric small arteries were cannulated in a dual-vessel chamber. After a 60-min equilibration period, the pressure in I artery was increased to 140 mm Hg, while the other artery remained at 90 mm Hg. Semiquant. reverse transcriptase-polymerase chain reaction was used to determine c-fos expression, and Western blotting was used to examine levels of ERK phosphorylation. The involvement of src and ERK was tested with the inhibitors herbimycin A (1 μmol/L), PP1 (10 μmol/L), PP2 (10 μmol/L), and PD98059 (30 μmol/L). One-hour exposure to 140 mm Hg increased the c-fos/cyclophilin ratio 3.6-fold, from 0.29±0.07 to 1.06±0.25. All the tested inhibitors suppressed the pressure-induced increase of c-fos expression. A 5-min exposure period to 140 mm Hg increased ERK phosphorylation, and this was abolished in the presence of PP1. The results suggest that pressure-induced c-fos expression in intact cannulated rat mesenteric small arteries may be mediated, at least in part, by src tyrosine kinases and ERK.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:153502 CAPLUS
DOCUMENT NUMBER: 134:324500
TITLE: Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension
AUTHOR(S): Taraseviciene-Stewart, Laimute; Kasahara, Yasunori; Alger, Lori; Hirth, Peter; McMahon, Gerald; Waltenberger, Johannes; Voelkel, Norbert F.; Tuder, Rubin M.
CORPORATE SOURCE: Department of Pathology, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: FASEB Journal (2001), 15(2), 427-438
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our understanding of the pathobiol. of severe pulmonary hypertension, usually a fatal disease, has been hampered by the lack of information of its natural history. We have demonstrated that, in human severe pulmonary hypertension, the precapillary pulmonary arteries show occlusion by proliferated endothelial cells. Vascular endothelial growth factor (VEGF) and its receptor 2 (VEGFR-2) are involved in proper maintenance, differentiation, and function of endothelial cells. We demonstrate here that VEGFR-2 blockade with SU5416 in combination with chronic hypobaric hypoxia causes severe pulmonary hypertension associated with precapillary arterial occlusion by proliferating endothelial cells. Prior to and concomitant with the development of severe pulmonary

hypertension, lungs of chronically hypoxic SU5416-treated rats show significant pulmonary endothelial cell death, as demonstrated by activated caspase 3 immunostaining and TUNEL. The broad caspase inhibitor Z-Asp-CH2-DCB prevents the development of intravascular pulmonary endothelial cell growth and severe pulmonary hypertension caused by the combination of SU5416 and chronic hypoxia.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:871656 CAPLUS
DOCUMENT NUMBER: 134:142996
TITLE: Tyrosine phosphorylation of cortactin is required for H2O2-mediated injury of human endothelial cells
AUTHOR(S): Li, Yansong; Liu, Jiali; Zhan, Xi
CORPORATE SOURCE: Department of Experimental Pathology, Holland Laboratory, American Red Cross, Rockville, MD, 20855, USA
SOURCE: Journal of Biological Chemistry (2000), 275(47), 37187-37193
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Injury of endothelial cells induced by reactive oxygen species plays an important role in the development of early stages of vascular diseases such as hypertension and atherosclerosis. Exposure of human umbilical vein endothelial cells to H2O2, a common form of reaction oxygen species, triggers a series of intracellular events, including actin cytoskeletal reorganization, cytoplasm shrinkage, membrane blebbing, and protein-tyrosine phosphorylation. The effect of H2O2 on endothelial cells is dramatically enhanced when a survival pathway involving extracellular signal-regulated kinase is blocked by PD098059. In contrast, the injury of endothelial cells mediated by H2O2 is inhibited by PP2, a selective specific inhibitor for protein-tyrosine kinase Src. Cortactin, a filamentous actin (F-actin)-associated protein, becomes phosphorylated at tyrosine residues upon stimulation by H2O2 in a manner dependent on the activity of Src. The level of tyrosine phosphorylation of cortactin is correlated with the formation of membrane blebs. Overexpression of wild-type cortactin tagged with green fluorescent protein in endothelial cells via a retroviral vector substantiates the H2O2-induced morphol. changes whereas overexpression of a green fluorescent protein-cortactin mutant deficient in tyrosine phosphorylation renders endothelial cells resistant to H2O2. The functional role of cortactin in H2O2-mediated shape changes was also evaluated in NIH 3T3 cells. Stable 3T3 transfectants expressing wild-type cortactin in the presence of either H2O2/PD098059 or H2O2 alone at 200 μM exhibited a dramatic shape change characterized by rounding up or aggregation. However, the similar changes were not detected with cells overexpressing a cortactin mutant deficient in tyrosine phosphorylation. These data demonstrate an important role of the Src /cortactin-dependent actin reorganization in the injury of endothelial cells mediated by reactive oxygen species.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:774308 CAPLUS
DOCUMENT NUMBER: 134:66636
TITLE: Angiotensin II stimulates extracellular

signal-regulated kinase activity in intact pressurized rat mesenteric resistance arteries

AUTHOR(S): Matrougui, K.; Eskildsen-Helmond, Y. E. G.; Fiebeler, A.; Henrion, D.; Levy, B. I.; Tedgui, A.; Mulvany, M. J.

CORPORATE SOURCE: Department of Pharmacology, University of Aarhus, Aarhus, DK-8000, Den.

SOURCE: Hypertension (2000), 36(4), 617-621
CODEN: HPRTDN; ISSN: 0194-911X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The activation of extracellular signal-regulated kinases 1/2 (ERK1/2) was assessed in isolated rat mesenteric resistance arteries (200-μm diameter) in a pressure myograph and stimulated for 5 min by angiotensin II (Ang II, 0.1 μM) with a pressure of 70 mm Hg. ERK1/2 activity was measured by using an in-gel assay, and ERK1/2 phosphorylation was measured by Western blot anal. with use of a phospho-specific ERK1/2 antibody. Ang II (0.1 μM) induced contraction (28% of phenylephrine contraction, 10 μM). ERK kinase inhibitor PD98059 (10 μM) attenuated this contraction by 36% but not that to phenylephrine or K+ (60 mmol/L). In unpressurized arteries, Ang II increased ERK1/2 activity by 26%, and pressure (70 mm Hg) itself increased ERK1/2 activity by 72%. Ang II and pressure together acted synergistically, increasing ERK1/2 activity by 264%. Thus, in pressurized vessels, Ang II (0.1 μM) increased ERK1/2 activity by 112%, calculated as [(364/172)-1]+100, which was confirmed by a measured 72% increase in ERK1/2 phosphorylation. Ang II type 1 receptor blockade by candesartan (10 μM) abolished the Ang II-induced increase in ERK1/2 activity, but Ang II type 2 receptor blockade (PD123319, 10 μM) did not. The Ang II-induced increase in ERK1/2 activity was inhibited by protein kinase C inhibitors Ro-31-8220 (1 μM) and Go-6976 (300 nmol/L) and tyrosine kinase inhibitors genistein (1 μM, general) and herbimycin A (1 μM, c- Src family). The present findings show for the first time in intact resistance arteries that ERK1/2 activation is rapidly regulated by Ang II, is synergistic with pressure, and is involved in contraction. The ERK1/2 signaling pathway apparently includes upstream protein kinase C and c-Src.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:69865 CAPLUS

DOCUMENT NUMBER: 132:220614

TITLE: Pressure-induced upregulation of preproendothelin-1 and endothelin B receptor expression in rabbit jugular vein in situ: implications for vein graft failure?

AUTHOR(S): Lauth, Manfred; Berger, Marc-Moritz; Cattaruzza, Marco; Hecker, Markus

CORPORATE SOURCE: Department of Cardiovascular Physiology, University of Goettingen, Goettingen, 37073, Germany

SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2000), 20(1), 96-103
CODEN: ATVBFA; ISSN: 1079-5642

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Upregulation of endothelin-1 (ET-1) synthesis in venous bypass grafts in response to arterial levels of blood pressure may play a major role in graft failure. To investigate this hypothesis, isolated segments of the rabbit jugular vein were perfused at physiol. (0 to 5 mm Hg) and nonphysiol. (20 mm Hg) levels of intraluminal pressure. As judged

by reverse transcription-polymerase chain reaction anal. (mRNA level), neither endothelin-converting enzyme nor endothelin A receptor expression appeared to be pressure sensitive. In contrast, there was a profound and time-dependent increase in endothelial prepro-ET-1 mRNA and intravascular ET-1 abundance (by ELISA) as well as in smooth muscle endothelin B receptor mRNA and functional protein (by superfusion bioassay) on raising the perfusion pressure from 5 to 20 mm Hg, but not from 0 to 5 mm Hg, for up to 12 h. Video microscopy anal. revealed that the segments were distended by 75% at 5 mm Hg and near maximally at 20 mm Hg compared with the resting diameter at 0 to 1 mm Hg. Treatment of the segments with actinomycin D (1 μM), the specific protein kinase C inhibitor , Ro 31-8220 (0.1 μM), or the c- Src family-specific tyrosine kinase inhibitor, herbimycin A (0.1 μM), demonstrated that the pressure-induced expression of these gene products occurs at the level of transcription and requires activation of protein kinase C, but not c-Src. In venous bypass grafts such deformation-induced changes in gene expression may contribute not only to acute graft failure through ET-1-induced vasospasm but also to endothelin A receptor- and/or endothelin B receptor-mediated smooth muscle cell hyperplasia and graft occlusion.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:69027 CAPLUS
DOCUMENT NUMBER: 130:262204
TITLE: Angiotensin II signal transduction in vascular smooth muscle: pathways activated by specific tyrosine kinases
AUTHOR(S): Berk, Bradford C.
CORPORATE SOURCE: Department of Medicine, Cardiology Unit, University of Rochester, Rochester, NY, 14642, USA
SOURCE: Journal of the American Society of Nephrology (1999), 10(1, Suppl. 11), S62-S68
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 64 refs., on the signal events regulated by angiotensin II (AngII) in vascular smooth muscle based on activation of specific tyrosine kinases. AngII has been shown to play a critical role in the pathogenesis of hypertension, inflammation, atherosclerosis, and congestive heart failure. The expanding role of AngII indicates that multiple signal transduction pathways are likely to be activated in a tissue-specific manner. Although at least three AngII receptors have been characterized, it seems that the AngII type I receptor (AT1R) is physiol. most important since pharmacol. inhibitors of the AT1R block most AngII signal events and have beneficial effects on cardiovascular disease. The AT1R is a seven transmembrane-spanning G protein-coupled receptor that regulates intracellular signal events by activation of Gq and Gi. However, many recent data indicate that activation of tyrosine kinases by several different mechanisms contributes to AngII effects in target tissues. Tyrosine kinases activated by AngII include c-Src, focal adhesion kinase (FAK), Pyk2 (CADTK), Janus kinases (JAK2 and TYK2), and the receptor tyrosine kinases Axl, epidermal growth factor, and platelet-derived growth factor. Finally, unknown tyrosine kinases may mediate tyrosine phosphorylation of paxillin, Shc, Raf, and phospholipase C-γ after AngII stimulation. These AngII-regulated tyrosine kinases seem to be required for AngII effects such as vasoconstriction, proto-oncogene expression, and protein synthesis based on studies with tyrosine kinase inhibitors. Thus, understanding AngII-stimulated signaling events, especially those related to tyrosine kinase

activity, may form the basis for the development of new therapies for cardiovascular diseases.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:309203 CAPLUS
DOCUMENT NUMBER: 129:76952
TITLE: Erythropoietin receptor-operated Ca2+ channels: Activation by phospholipase C-γ1
AUTHOR(S): Marrero, Mario B.; Venema, Richard C.; Ma, Heping; Ling, Brian N.; Eaton, Douglas C.
CORPORATE SOURCE: Renal Division and The Center for Cell and Molecular Signaling, Emory University School of Medicine and Veterans Affairs Medical Center, Atlanta, GA, USA
SOURCE: Kidney International (1998), 53(5), 1259-1268
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Erythropoietin (EPO) increases Ca2+ influx in vascular smooth muscle cells and acts both as a direct vasoconstrictor and vascular growth factor (i.e., angiogenesis). However, the mechanism by which EPO promotes extracellular Ca2+ entry in contractile cells has not been elucidated. In hematopoietic cells, EPO induces tyrosine kinase (TK)-dependent activation of phospholipase C (PLC)-γ1 and Ca2+ influx via a voltage-independent Ca2+ conductance. In contractile mesangial cells, the authors have recently characterized a voltage-independent, 1 pS Ca2+ channel that is dependent on both TK and PLC-γ1 activity. Therefore, the authors examined cultured rat glomerular mesangial cells after timed exposure to recombinant human EPO (20 U/mL). Erythropoietin increased the tyrosine phosphorylation of PLC-γ1, promoted membrane complex formation between PLC-γ1 and the EPO receptor itself, and raised the levels of intracellular inositol 1,4,5-trisphosphate and intracellular Ca2+. Consistent with the authors' previous studies, 1 pS Ca2+ channel activity was extremely low under basal, unstimulated conditions in cell-attached patches, but was dramatically increased when EPO was present in the patch pipet. Tyrosine kinase inhibition with 100 μM genistein or 1 μM PP1 (Src; selective tyrosine kinase inhibitor) prevented all of these EPO-induced responses. The authors conclude that: (1) EPO-induced stimulation of 1 pS Ca2+ channels is mediated via a cytosolic Src TK in glomerular mesangial cells. (2) Stimulation of this Ca2+-activated, Ca2+-permeable channel is dependent on the tyrosine phosphorylation/activation of PLC-γ1. (3) This cascade provides a possible mechanism for the vasoconstriction and hypertension observed with clin. EPO use for the treatment of chronic anemias.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:791871 CAPLUS
DOCUMENT NUMBER: 128:100595
TITLE: Increased pressure induces sustained protein kinase C-independent herbimycin A-sensitive activation of extracellular signal-related kinase 1/2 in the rabbit aorta in organ culture
AUTHOR(S): Birukov, Konstantin G.; Lehoux, Stephanie; Birukova, Anna A.; Merval, Regine; Tkachuk, Vsevolod A.; Tedgui, Alain
CORPORATE SOURCE: Laboratory of Molecular Endocrinology, Cardiology

Research Center, Moscow, Russia
SOURCE: Circulation Research (1997), 81(6), 895-903
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 42- and 44-kD mitogen-activated protein kinases, also referred to as extracellular signal-related kinase (ERK) 2 and 1, resp., may be transiently activated by stretching vascular smooth muscle cells (VSMCs). Using an organ culture model of rabbit aorta, the authors studied short- and long-term ERK1/2 activation by intraluminal pressure (150 mm Hg). Activation of ERK1/2 was biphasic: it reached a maximum (217.5% of control) 5 min after pressurizing and decreased to 120.7% of control after 2 h. Furthermore, after 24 h of pressurizing, ERK1/2 activity was as high (241.8% of control) as in the acute phase. Long-term pressure-induced ERK1/2 activation correlated with stimulation of tyrosine phosphorylation of proteins in the 125- to 140-kD range. Neither protein kinase C inhibitors (1 μmol/L staurosporine or 50 μmol/L bisindolylmaleimide-I) nor tyrosine kinase inhibitors (50 μmol/L tyrphostin A48 or 50 μmol/L genistein) affected pressure-induced ERK1/2 activation. However, the Src-family tyrosine kinase inhibitor herbimycin A (500 nmol/L) did reduce both 5-min (by 92±8%) and 24-h (by 63±7%) pressure-induced ERK1/2 activation. Thus, the results demonstrate a sustained activation of ERK1/2 and tyrosine kinases by intraluminal pressure in the arterial wall. Pressure-induced ERK1/2 activation is PKC independent and Src -family tyrosine kinase dependent and possibly includes activation of extracellular matrix-associated tyrosine kinases.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

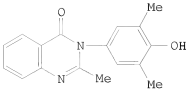
L5 ANSWER 24 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:287515 CAPLUS
DOCUMENT NUMBER: 127:827
TITLE: Angiotensin II signal transduction in vascular smooth muscle: role of tyrosine kinases
AUTHOR(S): Berk, Bradford C.; Corson, Marshall A.
CORPORATE SOURCE: Dep. Med., Cardiology Div., Univ. Washington, Seattle, WA, USA
SOURCE: Circulation Research (1997), 80(5), 607-616
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 119 refs., on the role of tyrosine kinases in angiotensin II-mediated signal transduction pathways in vascular smooth muscle. Angiotensin II was isolated by virtue of its vasoconstrictor abilities and has long been thought to play a critical role in hypertension. However, recent studies indicate important roles for angiotensin II in inflammation, atherosclerosis, and congestive heart failure. The expanding role of angiotensin II indicates that multiple signal transduction pathways are likely to be activated in a tissue-specific manner. Exciting recent data show that angiotensin II directly stimulates tyrosine kinases, including pp60c-src kinase (c-Src), focal adhesion kinase (FAK), and Janus kinases (JAK2 and TYK2). Angiotensin II may activate receptor tyrosine kinases, such as Axl and platelet-derived growth factor, by as-yet-undefined autocrine mechanisms. Finally, unknown tyrosine kinases may mediate tyrosine phosphorylation of Shc, Raf, and phospholipase C-γ after angiotensin II stimulation. These angiotensin II-regulated tyrosine kinases appear to be required for angiotensin II effects, such as vasoconstriction, proto-oncogene expression, and protein synthesis, on the basis of studies with tyrosine

kinase inhibitors. Thus, understanding angiotensin II-stimulated signaling events, especially those related to tyrosine kinase activity, may form the basis for the development of new therapies for cardiovascular diseases.

REFERENCE COUNT: 119 THERE ARE 119 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:232848 CAPLUS
DOCUMENT NUMBER: 124:279235
TITLE: Angiotensin II signaling events mediated by tyrosine phosphorylation
AUTHOR(S): Marrero, Mario B.; Paxton, William G.; Schieffer, Berhhard; Ling, Brian N.; Bernstein, Kenneth E.
CORPORATE SOURCE: Departments of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, 30322, USA
SOURCE: Cellular Signalling (1996), 8(1), 21-6
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 30 refs. Angiotensin II is a potent vasoconstrictor that is important in the control of systemic blood pressure. All the hemodynamic effects of angiotensin II result from the AT1 receptor which has the structural features of a seven transmembrane receptor. Both in cultured rat aortic smooth muscle cells and rat glomerular mesangial cells, angiotensin II stimulates the rapid tyrosine phosphorylation of phospholipase C-γ1 (PLC-γ1). Tyrosine kinase inhibitors that block this phosphorylation also block the angiotensin II-mediated production of 1,4,5 inositol trisphosphate (1,4,5-IP3) and the intracellular release of Ca2+. The cellular tyrosine kinase c-src appears to play a critical role in the angiotensin II-stimulated tyrosine phosphorylation of PLC-γ1 and the generation of 1,4,5-IP3. We have also found that angiotensin II stimulates the tyrosine phosphorylation and activation of the JAK family of intracellular kinases. This in turn activates the STAT family of transcription factors. Angiotensin II, working through the AT1 receptor, uses tyrosine phosphorylation as a mechanism to convey signals from the cell surface to the cell nucleus.

L5 ANSWER 26 OF 66 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1977:50499 CAPLUS
DOCUMENT NUMBER: 86:50499
ORIGINAL REFERENCE NO.: 86:7989a,7992a
TITLE: Some pharmacological studies on 2-methyl-3-(3,5-dimethyl-4-hydroxyphenyl)-3,4-dihydroquinazolin-4-one (SRC-226) and its derivatives
AUTHOR(S): Parikh, S. H.; Shah, G. F.; Nadkarni, A. S.; Radhakrishnan, A. V.
CORPORATE SOURCE: Dep. Pharmacol., Sarabhai Res. Cent., Baroda, India
SOURCE: Indian Journal of Pharmacy (1976), 38(3), 89-90
CODEN: IJPAAO; ISSN: 0019-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB SRC 226 [2-methyl-3-(3,5-dimethyl-4-hydroxyphenyl)-3,4-dihydroquinazolin-4-one](I) [27945-43-3] injected i.v. into dogs decreased blood pressure transiently and depressed respiration. The analgesic and antiinflammatory activities of I were 4 and 1.5 times greater, resp., than those of aspirin. The analgesic activity of 6 I derivs. was less than that of I.

L5 ANSWER 27 OF 66 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003257410 EMBASE
TITLE: Scleroderma renal crisis.
AUTHOR: Steen V.D.
CORPORATE SOURCE: Dr. V.D. Steen, Div. of Rheumatol., Immunol./Allergy, Department of Medicine, Georgetown University, 3800 Reservoir Road, Washington, DC 20007, United States. steenv@georgetown.edu
SOURCE: Rheumatic Disease Clinics of North America, (May 2003) Vol. 29, No. 2, pp. 315-333.
Refs: 75
ISSN: 0889-857X CODEN: RDCAEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
028 Urology and Nephrology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Jul 2003
Last Updated on STN: 17 Jul 2003

AB Renal crisis occurs in patients who have systemic sclerosis with rapidly progressive diffuse cutaneous thickening early in their disease. SRC is characterized by malignant hypertension, hyperreninemia, azotemia, microangiopathic hemolytic anemia, and renal failure. SRC was almost uniformly fatal, but in most cases it can now be successfully treated with ACE inhibitors. This therapy has improved survival, reduced the requirement for dialysis, and often allowed for the discontinuation of dialysis 6 to 18 months later. Prompt diagnosis and early, aggressive initiation of therapy with ACE inhibitors will result in the most optimal outcome.

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ACCESSION NUMBER: 2003037749 EMBASE
TITLE: Stretch enhances contraction of bovine coronary arteries via an NAD(P)H oxidase-mediated activation of the extracellular signal-regulated kinase mitogen-activated protein kinase cascade.
AUTHOR: Oeckler R.A.; Kaminski P.M.; Wolin M.S.
CORPORATE SOURCE: mike_wolin@nymc.edu
SOURCE: Circulation Research, (10 Jan 2003) Vol. 92, No. 1, pp. 23-31.

Refs: 37
ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
002 Physiology
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 2003
Last Updated on STN: 30 Jan 2003

AB This study examines the effects of an increase in passive stretch in endothelium-removed bovine coronary artery on oxidant-induced changes in force generation. Increasing passive stretch on the arterial segments from 5 to 20 g for 20 minutes caused a subsequent increase ($P<0.05$) in force generation to 30 mmol/L KCl or 0.1 μmol/L serotonin compared with the prestretch control response. Also associated with the passive stretch were increases in superoxide detection by lucigenin and a selective increase in extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase phosphorylation measured by Western analysis. The stretch-induced increase in force generation was eliminated by inhibition of the ERK pathway by the MEK inhibitor PD98059 but not by inhibitors of the p38 MAP kinase pathway (SB202190) or c-Jun N-terminal protein kinase pathway (SP200169). Additionally, stretch-induced increases in both ERK phosphorylation and force generation were attenuated by inhibition of tyrosine kinases (genistein), src (PP2), and specific sites on the epidermal growth factor receptor (EGFR) (AG1478). Probes for oxidant signaling, including NAD(P)H oxidase inhibitors (diphenyliodonium and apocynin) or enhancement of peroxide consumption (ebselen) but not inhibition of xanthine oxidase (allopurinol), attenuated the effects of stretch on both ERK phosphorylation and force generation. Furthermore, stretch caused an increase in EGFR phosphorylation and cytosolic to membrane translocation of the p47phox NAD(P)H oxidase subunit. Hydrogen peroxide also elicited contraction through EGFR phosphorylation and ERK. In summary, stretch seems to enhance force generation via ERK signaling through an EGFR/src-dependent mechanism activated by peroxide derived from a stretch-mediated activation of the NAD(P)H oxidase, a response that may contribute to hypertensive alterations in vascular reactivity.

L5 ANSWER 29 OF 66 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002336412 EMBASE
TITLE: Tyrosine kinases regulate intracellular calcium during α(2)-adrenergic contraction in rat aorta.
AUTHOR: Carter R.W.; Kanagy N.L.
CORPORATE SOURCE: R.W. Carter, Vasc. Physiology Research Division, Dept. of Cell Biology, Univ. of New Mexico Hlth. Sci. Ctr., 915 Camino de Salud, Albuquerque, NM 87131-5218, United States. bcarter@salud.unm.edu
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (Oct 2002) Vol. 283, No. 4 52-4, pp. H1673-H1680.
Refs: 41
ISSN: 0363-6135 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 10 Oct 2002
Last Updated on STN: 10 Oct 2002

AB We have demonstrated enhanced contractile sensitivity to the α(2)-adrenoreceptor (α(2)-AR) agonist UK-14304 in arteries from rats made hypertensive with chronic nitric oxide synthase (NOS) inhibition (LHR) compared with arteries from normotensive rats (NR); additionally, this contraction requires Ca(2+) entry. We hypothesized that tyrosine kinases augment α(2)-AR contraction in LHR arteries by increasing Ca(2+). The tyrosine kinase inhibitor tyrphostin 23 significantly attenuated UK-14304 contraction of denuded thoracic aortic rings from NR and LHR. However, tyrphostin 23 did not alter UK-14304 contraction in ionomycin-permeabilized aorta, which indicates that tyrosine kinases regulate intracellular Ca(2+) concentration. The Src family inhibitor PP1 and the epidermal growth factor receptor kinase inhibitor AG-1478 did not alter α(2)-AR contraction, whereas the mitogen-activated protein kinase extracellular signal-regulated kinase kinase inhibitor PD-98059 attenuated the contraction. Contraction to CaCl(2) in ionomycin-permeabilized LHR rings was greater than in NR rings. UK-14304 augmented CaCl(2) contraction in ionomycin-permeabilized rings from both groups but to a greater extent in LHR aorta. Together, these data suggest that α(2)-AR stimulates contraction via two pathways. One, which is enhanced with NOS inhibition hypertension, activates Ca(2+) sensitivity and is independent of tyrosine kinases. The other is tyrosine kinase dependent and regulates intracellular Ca(2+) concentration.

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ACCESSION NUMBER: 2001248717 EMBASE
TITLE: Systemic sclerosis with renal crisis and pulmonary hypertension: A report of eleven cases.
AUTHOR: Gundtiz O.H.; Fertig N.; Lucas M.; Medsger T.A. Jr.
CORPORATE SOURCE: Dr. T.A. Jr. Medsger, 7 South Biomedical Science Tower, 3500 Terrace Street, Pittsburgh, PA 15261, United States
SOURCE: Arthritis and Rheumatism, (2001) Vol. 44, No. 7, pp. 1663-1666.
Refs: 11
ISSN: 0004-3591 CODEN: ARHEAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
028 Urology and Nephrology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2001
Last Updated on STN: 2 Aug 2001

AB Objective. To describe a series of systemic sclerosis (SSc) patients with the unusual combination of scleroderma renal crisis (SRC) and pulmonary hypertension (PHT) without interstitial lung disease. Methods. The medical records of 2,459 SSc patients in the University of Pittsburgh Scleroderma Databank first evaluated between 1972 and 1999 were reviewed. Results. Eleven patients (0.45%) had both SRC and PHT. All had been evaluated since 1979, when angiotensin-converting enzyme (ACE) inhibitor therapy for SRC became available. Seven had SSc with limited cutaneous involvement, and 4 had SSc with diffuse cutaneous involvement. SRC occurred first in all patients except 1, in whom the onsets of SRC and PHT were simultaneous. SRC preceded PHT by a mean of 4.3 years. Four patients had anti-Th/To antibody, 5 had anti-RNA polymerase III antibody,

2 had anti-U3 RNP antibody, and none had anticentromere or antitopoisomerase I antibody. Ten of the 11 patients died, 8 from PHT. Ten patients were being treated with ACE inhibitor drugs when PHT developed. Conclusion. In SSc, SRC and PHT are not mutually exclusive complications. SSc patients surviving SRC who have serum antibodies to Th/To, RNA polymerase III, or U3 RNP are at increased risk to develop PHT. ACE inhibitor therapy did not prevent the development of PHT.

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ACCESSION NUMBER: 2001148859 EMBASE
TITLE: Thrombotic thrombocytopenia purpura in a patient with systemic sclerosis.
AUTHOR: Yusin J.; Lewin K.; Clements P.
CORPORATE SOURCE: Dr. J. Yusin, Medical Center Phoenix, Department of Medicine, Sec. of Allergy and Immunology (III), 650 East Indian School Road, Phoenix, AZ 85012, United States
SOURCE: Journal of Clinical Rheumatology, (2001) Vol. 7, No. 2, pp. 106-111.
Refs: 15
ISSN: 1076-1608 CODEN: JCRHFM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
048 Gastroenterology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 May 2001
Last Updated on STN: 10 May 2001

AB Thrombotic thrombocytopenic purpura (TTP) has been associated with scleroderma renal crises (SRC) in the past. However such reports markedly diminished after the onset of ACE inhibitor use. Recently, reports again have surfaced that describe scleroderma patients presenting with clinical evidence of TTP. We describe a 50-year-old female with longstanding limited cutaneous scleroderma who presented with hematochezia and thrombocytopenia along with other findings suggesting TTP. A colon biopsy revealed thrombi within the lumen. Her course was complicated by renal failure and hypertension that did not respond to ACE inhibitor therapy alone. She improved after a course of plasma exchange. She was discharged home only to return 2 months later with grand mal seizures and hypertension. During her course she developed adult respiratory distress syndrome. She again responded to plasma exchange and she was discharged home. She has remained stable for 2 years. This report emphasizes the importance of fully evaluating patients with longstanding limited cutaneous scleroderma who present with renal failure, hypertension, and thrombocytopenia in association with multiorgan complications. All possible etiologies, including SRC, TTP, vasculitis, and sepsis should be considered. Tissue biopsies (in this case, a colon biopsy revealed thrombi within the vessel lumen) may prove beneficial in assisting with the diagnosis. For such patients who fail treatment with ACE inhibitors, plasma exchange may be considered.

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ACCESSION NUMBER: 2000234942 EMBASE
TITLE: Ramipril increases the protein level of skeletal muscle IRS-1 and alters protein tyrosine phosphatase activity in spontaneously hypertensive rats.

AUTHOR: Krutzfeldt J.; Raasch W.; Klein H.H.
CORPORATE SOURCE: H.H. Klein, Medizinische Klinik 1, Medical University of Lubeck, Ratzeburger Allee 160, D-23538 Lubeck, Germany. klein@medinf.mu-luebeck.de
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology, (2000) Vol. 362, No. 1, pp. 1-6.
Refs: 42
ISSN: 0028-1298 CODEN: NSAPCC
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jul 2000
Last Updated on STN: 20 Jul 2000

AB To investigate mechanisms by which angiotensin converting enzyme (ACE)-inhibition increases insulin sensitivity, spontaneously hypertensive (SH) rats were treated with or without ramipril (1 mg/kg per day) for 12 weeks. Insulin binding and protein levels of insulin receptor substrate-1 (IRS-1), p85-subunit of phosphatidylinositol 3'-kinase (p85) and Src homology 2 domain-containing phosphatase-2 (SHP2) were then determined in hindlimb muscle and liver. Additionally, protein tyrosine phosphatase (PTPase) activities towards immobilized phosphorylated insulin receptor or phosphorylated IRS-1 of membrane (MF) and cytosolic fractions (CF) of these tissues were measured. Ramipril treatment increased IRS-1-protein content in muscle by 31 ± 9% ($P < 0.05$). No effects were observed on IRS-1 content in liver or on insulin binding or protein expression of p85 or SHP2 in both tissues. Ramipril treatment also increased dephosphorylation of insulin receptor by muscle CF (22.0 ± 1.0%/60 min compared to 16.8 ± 1.5%/60 min; $P < 0.05$), and of IRS-1 by liver MF (37.2 ± 1.7%/7.5 min compared to 33.8 ± 1.7%/7.5 min: $P < 0.05$) and CF (36.8 ± 1.0%/7.5 min compared to 33.2 ± 1.0%/7.5 min; $P < 0.05$). We conclude that the observed effects of ACE- inhibition by ramipril on the protein expression of IRS-1 and on PTPase activity might contribute to its effect on insulin sensitivity.

L5 ANSWER 33 OF 66 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000136454 EMBASE
TITLE: Successful use of angiotensin II receptor antagonist(losartan) in a patient with scleroderma renal crisis.
AUTHOR: Kondou Y.
CORPORATE SOURCE: S. Hasegawa, Department of Nephrology, Chiba Social Insurance Hospital, Chiba, Japan
SOURCE: Japanese Journal of Nephrology, (2000) Vol. 42, No. 2, pp. 60-65.
Refs: 3
ISSN: 0385-2385 CODEN: NJGKAU
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 4 May 2000
Last Updated on STN: 4 May 2000

AB A 67-year-old man with a one-and-a half-year history of Raynaud's phenomenon was admitted to our hospital for progressive dyspnea occurring over the previous two weeks. Physical examination revealed a blood pressure of 200/124 mmHg, and slightly tight and

smooth skin of the fingers, hands and forearms. Laboratory evaluation included serum creatinine of 5.42 mg/dl, plasma renin activity > 20 ng/ml/hr, and antinuclear antibody with a titer of 1 : 1,280. Renal biopsy was performed and the histopathological findings showed that some glomeruli exhibited ischemic retraction with wrinkling of the basement membranes, and that one arteriole exhibited significant intimal hyperplasia with luminal stenosis. These findings were compatible with scleroderma renal crisis (SRC). On the 5th day, serum creatinine had risen to 9.16 mg/dl, and he required temporary hemodialysis therapy. After the administration of captopril was started, his blood pressure fell to 160/86 mmHg and serum creatinine was reduced to 5.12 mg/dl. On the 9th day, he exhibited skin eruptions, and captopril was discontinued accordingly and temocapril started. Because of continued eruptions, temocapril was replaced by losartan. His blood pressure was controlled easily and his serum creatinine level reduced steadily. One year after the start of losartan, serum creatinine was 2.25 mg/dl and blood pressure was 130/82 mmHg. SRC is a life-threatening manifestation of systemic sclerosis. In the late 1970s, angiotensin converting enzyme (ACE) inhibitor was introduced and has dramatically improved the outcome in SRC patients. As ACE inhibitors act mainly on hyperreninemic renal vasoconstrictive hypertension in SRC, we would expect losartan, a selective antagonist of angiotensin receptor subtype 1, to be interchangeable with ACE inhibitors in SRC. In 1997, Caskey and colleagues reported the failure of losartan to control hypertension in a patient of SRC, and the reason has remained unclear. We report here, a case of SRC whose blood pressure was controlled successfully and his renal failure reversed by the administration of losartan.

L5 ANSWER 34 OF 66 EMBASE

ACCESSION NUMBER: 1999050267 EMBASE

TITLE: Involvement of PYK2 in angiotensin II signaling of vascular smooth muscle cells.

AUTHOR: Eguchi S.; Iwasaki H.; Inagami T.; Numaguchi K.; Yamakawa T.; Motley E.D.; Owada K.M.; Marumo F.; Hirata Y.

CORPORATE SOURCE: Dr. S. Eguchi, 2nd Department of Internal Medicine, Tokyo Medical/Dental University, 1-5-45 Yushima, Bunkyo-Ku, Tokyo 113-8519, Japan. seguchi.med2@med.tmd.ac.jp

SOURCE: Hypertension, (Jan 1999) Vol. 33, No. 1 II, pp. 201-206. Refs: 33
ISSN: 0194-911X CODEN: HPRTDN

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 4 Mar 1999
Last Updated on STN: 4 Mar 1999

AB PYK2, a recently identified Ca(2+)-sensitive tyrosine kinase, has been implicated in extracellular signal-regulated kinase (ERK) activation via several G protein-coupled receptors. We have reported that angiotensin II (Ang II) induces Ca(2+)-dependent transactivation of the epidermal growth factor receptor (EGFR) which serves as a scaffold for preactivated c-Src and downstream adaptors (Shc/Grb2), leading to ERK activation in cultured rat vascular smooth muscle cells (VSMC). Herein we demonstrate the involvement of PYK2 in this cascade. Ang II rapidly induced tyrosine phosphorylation of PYK2, whose effect was completely

inhibited by an AT(1) receptor antagonist and an intracellular Ca(2+) chelator. A Ca(2+) ionophore also induced PYK2 tyrosine phosphorylation to a level comparable with that by Ang II, whereas phorbol ester-induced phosphorylation was less than that by Ang II. Moreover, PYK2 formed a complex coprecipitable with catalytically active c-Src after Ang II stimulation. Although a selective EGFR kinase inhibitor completely abolished Ang II-induced recruitment of Grb2 to EGFR and markedly attenuated Ang II-induced ERK activation, it had no effect on Ang II-induced PYK2 tyrosine phosphorylation or its association with c-Src and Grb2. These data suggest that the AT(1) receptor uses Ca(2+)-dependent PYK2 to activate c-Src, thereby leading to EGFR transactivation, which preponderantly recruits Grb2 in rat VSMC.

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ACCESSION NUMBER: 1999044138 EMBASE
TITLE: Role of tissue angiotensin II in myocardial remodelling induced by mechanical stress.
AUTHOR: Yamazaki T.; Yazaki Y.
CORPORATE SOURCE: T. Yamazaki, Department Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
SOURCE: Journal of Human Hypertension, (1999) Vol. 13, No. SUPPL. 1, pp. S43-S47.
Refs: 32
ISSN: 0950-9240 CODEN: JHHYEN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
003 Endocrinology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Feb 1999
Last Updated on STN: 11 Feb 1999

AB In an in vivo study, spontaneously hypertensive rats (SHR) were treated with an angiotensin II (Ang II) type 1 receptor antagonist of candesartan or hydralazine. Untreated SHR progressively developed severe hypertension, and treatment with candesartan or hydralazine decreased blood pressure. Candesartan reduced left ventricular (LV) weight, LV wall thickness, transverse myocyte diameter, the relative amount of V3 myosin heavy chain, and interstitial fibrosis, while treatment with hydralazine slightly prevented an increase in LV wall thickness, but did not exert a significant reduction on other parameters. In an in vitro study, neonatal rat cardiomyocytes were cultured on deformable silicone dishes. Stretching cardiomyocytes activated second messengers such as protein kinase C, Raf-1 kinase, and mitogen-activated protein (MAP) kinase, increasing protein synthesis, enhancing endothelin (ET)-1 release, activating the Na(+)/H(+) ion exchanger. Moreover, pretreatment with candesartan diminished an increase in phenylalanine incorporation, MAP kinase activity, and c-fos gene expression induced by the stretching of cardiomyocytes. This suggests that the cardiac renin-angiotensin system is linked to the formation of pressure-overload hypertrophy and that Ang II increases the growth of cardiomyocytes by an autocrine mechanism. Finally, we examined the signalling pathways leading to MAP kinase activation both in cardiac myocytes and in cardiac fibroblasts. Ang II-evoked signal transduction pathways differed between cell types. In cardiac fibroblasts, Ang II activated MAP kinase through a pathway including the Gβγ subunit of Gi protein, Src, Shc, Grb2, and Ras, while Gq and protein kinase C were important in cardiac myocytes.

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ACCESSION NUMBER: 1999029652 EMBASE
TITLE: Angiotensin II signal transduction in vascular smooth muscle: Pathways activated by specific tyrosine kinases.
AUTHOR: Berk B.C.
CORPORATE SOURCE: Dr. B.C. Berk, Cardiology Unit, Box 679, Univ. of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, United States
SOURCE: Journal of the American Society of Nephrology, (Jan 1999) Vol. 10, No. 1 SUPPL. 11, pp. S62-S68.
Refs: 64
ISSN: 1046-6673 CODEN: JASNEU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Feb 1999
Last Updated on STN: 11 Feb 1999

AB In this review, the signal events regulated by angiotensin II (AngII) in vascular smooth muscle are analyzed based on activation of specific tyrosine kinases. AngII has been shown to play a critical role in the pathogenesis of hypertension, inflammation, atherosclerosis, and congestive heart failure. The expanding role of AngII indicates that multiple signal transduction pathways are likely to be activated in a tissue-specific manner. Although at least three AngII receptors have been characterized, it seems that the AngII type 1 receptor (AT1R) is physiologically most important since pharmacologic inhibitors of the AT1R block most AngII signal events and have beneficial effects on cardiovascular disease. The AT1R is a seven transmembrane-spanning G protein-coupled receptor that regulates intracellular signal events by activation of G(q) and G(i). However, many recent data indicate that activation of tyrosine kinases by several different mechanisms contributes to AngII effects in target tissues. Tyrosine kinases activated by AngII include c-Src, focal adhesion kinase (FAK), Pyk2 (CADTK), Janus kinases (JAK2 and TYK2), and the receptor tyrosine kinases Axl, epidermal growth factor, and platelet-derived growth factor. Finally, unknown tyrosine kinases may mediate tyrosine phosphorylation of paxillin, Shc, Raf, and phospholipase C-γ after AngII stimulation. These AngII-regulated tyrosine kinases seem to be required for AngII effects such as vasoconstriction, proto-oncogene expression, and protein synthesis based on studies with tyrosine kinase inhibitors. Thus, understanding AngII-stimulated signaling events, especially those related to tyrosine kinase activity, may form the basis for the development of new therapies for cardiovascular diseases.

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ACCESSION NUMBER: 1998214268 EMBASE
TITLE: Angiotensin II stimulates p21-activated kinase in vascular smooth muscle cells: Role in activation of JNK.
AUTHOR: Schmitz U.; Ishida T.; Ishida M.; Surapisitchat J.; Hasham M.I.; Pelech S.; Berk B.C.
CORPORATE SOURCE: B.C. Berk, Division of Cardiology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, United States. bcberk@u.washington.edu
SOURCE: Circulation Research, (29 Jun 1998) Vol. 82, No. 12, pp. 1272-1278.
Refs: 39

ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jul 1998
Last Updated on STN: 30 Jul 1998

AB Angiotensin II (Ang II) has been previously shown to stimulate the extracellular signal-regulated kinase (ERK) 1/2 and c-Jun N-terminal kinase (JNK) mitogen-activated protein (MAP) kinase family members. Little is known regarding the upstream signaling molecules involved in Ang II-mediated JNK activation. Ang II has been shown to activate the Janus kinase/signal transducer(s) and activator(s) of transcription (JAK/STAT) pathway, suggesting similarities to cytokine signaling. In response to cytokines such as interleukin-1 and tumor necrosis factor-a, the p21-activated kinase (PAK) has been identified as an upstream component in JNK activation. Therefore, we hypothesized that PAK may be involved in JNK activation by Ang II in vascular smooth muscle cells (VSMCs). αPAK activity was measured by myelin basic protein phosphorylation in rat aortic VSMCs. In response to Ang II, αPAK was rapidly stimulated within 1 minute, with a peak (5-fold increase) at 30 minutes. αPAK stimulation preceded activation of JNK in VSMCs. Ang II-mediated activation of both aPAK and JNK was Ca(2+) dependent and inhibited by downregulation of phorbol ester-sensitive protein kinase C isoforms (by pretreatment with phorbol 12,13-dibutyrate) but not by pretreatment with GF109203X. Activation of both PAK and JNK was partially inhibited by tyrosine kinase inhibitors but not by specific Src inhibitors, suggesting regulation by a tyrosine kinase other than c-Src. Finally, introduction of dominant negative PAK markedly reduced the JNK activation by Ang II in both Chinese hamster ovary and COS cells stably expressing the Ang II type 1 receptor (AT1R). Our data provide evidence for aPAK as an upstream mediator of JNK in Ang II signaling and extend the role of Ang II as a proinflammatory mediator for VSMCs.

L5 ANSWER 38 OF 66 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997295136 EMBASE
TITLE: A patient with systemic scleroderma showing improvement during long- term hemodialysis after renal crisis.
AUTHOR: Fuse Y.; Muramatsu M.; Sugiyama S.; Maeda K.
CORPORATE SOURCE: Y. Fuse, Tohkai Clinic, Tokai-city, Japan
SOURCE: Ryumachi, (1997) Vol. 37, No. 4, pp. 574-580.
Refs: 22
ISSN: 0300-9157 CODEN: RYMCAF
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 30 Oct 1997
Last Updated on STN: 30 Oct 1997

AB A 68-year-old man experienced systemic pruritus since he was 63 years old, and systemic sclerosis and skin pigmentation were observed when he was 64. When he developed dyspnea the same year, he was admitted and SSc was diagnosed on the basis of the clinical and skin biopsy findings, lung fibrosis on X-P and TBLB findings. At 65, his dyspnea reappeared along

with elevated blood pressure, acute renal failure and lung congestion, and he was diagnosed as having a scleroderma renal crisis (SRC) from the clinical and renal biopsy findings. Hemodialysis was started because he showed mental disturbance, and this and other acute symptoms were subsequently reduced. As he showed no recovery from his renal failure, the patient has been maintained on hemodialysis for over four years now. In the meantime, his sclerosis has improved and antinuclear antibody almost disappeared. Hemodialysis appears to be the most likely reason for his improvement, although spontaneous remission, D-penicillamine and angiotensin converting enzyme (ACE) inhibitor therapy may also have contributed, considering the short period and the small amount of drugs given until improvement.

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ACCESSION NUMBER: 1997266706 EMBASE
TITLE: Scleroderma renal crisis analysis of prevalence and outcome in a large italian series.
AUTHOR: La Montagna G.; Baruffo A.; Maja L.; Tirri E.; Matrone C.; Vatti M.; Valentini G.
CORPORATE SOURCE: Dr. G. La Montagna, via F Cast, Idi, 26 80011 Acerra (NA), Italy
SOURCE: Journal of Clinical Rheumatology, (Aug 1997) Vol. 3, No. 4, pp. 188-193.
Refs: 25
ISSN: 1076-1608 CODEN: JCRHFM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
028 Urology and Nephrology
005 General Pathology and Pathological Anatomy
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Sep 1997
Last Updated on STN: 25 Sep 1997

AB During a 30-year period, 323 SSc patients were admitted to a tertiary center specialized in connective tissue diseases. Among them 13 (4%) developed scleroderma renal crisis (SRC). These 13 SRC patients with respect to the remaining SSc patients were older, were more often affected by diffuse cutaneous systemic sclerosis (dcSSc), and had slightly higher blood pressure and more frequent heart involvement at initial presentation. Among the 13 SRC patients, an older age, a shorter disease duration, and a higher peak serum creatinine correlated with a poor outcome. SRC in Italian patients showed a lower prevalence (4%) than in many earlier reports. Mean survival in SRC patients was 6 years. This tended to be less than the 16.5 years for all others, but this trend was not statistically significant at least for those admitted in the post-captopril era. From a clinical point of view, the higher prevalence of later SRC in dcSSc patients presenting with mild arterial hypertension and or heart involvement is worth noting. Many patients were asymptomatic and were detected only on a routine visit. Such patients must be carefully followed to detect any early finding of SRC.

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ACCESSION NUMBER: 1996361022 EMBASE
TITLE: Scleroderma renal crisis.
AUTHOR: Steen V.D.
CORPORATE SOURCE: V.D. Steen, Div. Rheumatology Immunology Allergy,

Georgetown University Medical Center, LL Gorman Building, 3800 Reservoir Road NW, Washington, DC 20007-2197, United States
SOURCE: Rheumatic Disease Clinics of North America, (1996) Vol. 22, No. 4, pp. 861-878.
ISSN: 0889-857X CODEN: RDCAEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 028 Urology and Nephrology
031 Arthritis and Rheumatism
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Dec 1996
Last Updated on STN: 18 Dec 1996

AB Renal crisis occurs in systemic sclerosis patients with rapidly progressive diffuse cutaneous thickening early in their disease. SRC is characterized by malignant hypertension, hyperreninemia, azotemia, microangiopathic hemolytic anemia, and renal failure. This complication, which in the past has been almost uniformly fatal, is now successfully treated in most cases with ACE inhibitors. This therapy has improved survival, reduced requirement for dialysis, and in those on dialysis has often allowed discontinuation of this procedure 6 to 18 months later. Prompt diagnosis and early, aggressive initiation of therapy with ACE inhibitors will result in the most optimal outcome. Chronic nonrenal crisis renal insufficiency is unusual and rarely progresses to significant renal dysfunction.

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ACCESSION NUMBER: 1996336849 EMBASE
TITLE: [Sclerodermal renal crisis].
INSUFFICIENZA RENALE ACUTA IN CORSO DI SCLEROSI SISTEMICA PROGRESSIVA.
AUTHOR: Stratta P.; Besso L.; Ferrero S.; Canavese C.; Hollo S.; Ottone S.; Sandri L.; Thea A.; Mazzucco G.
CORPORATE SOURCE: P. Stratta, Cattedra di Nefrologia, Universita di Torino, Corso A.M. Dogliotti, 14, 10126 Torino, Italy
SOURCE: Gazzetta Medica Italiana Archivio per le Scienze Mediche, (Apr 1996) Vol. 155, No. 2, pp. 57-61.
Refs: 20
ISSN: 0393-3660 CODEN: GMIMES
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: Italian
SUMMARY LANGUAGE: English; Italian
ENTRY DATE: Entered STN: 10 Dec 1996
Last Updated on STN: 10 Dec 1996

AB Sclerodermal renal crisis (SRC) was known as a rare and catastrophic syndrome responsible for acute renal failure (ARF) in a context of widespread microvascular disease occurring in progressive systemic sclerosis (PSS). Following pathogenic hypothesis, angiotensin converting enzyme (ACE) inhibitors, plasma infusion (PI) and plasma-exchange (PE) have been employed in SRC with favourable results. Our purpose was to verify whether these therapies have

consistently changed the fatal prognosis of SRC even in our experience. In the last ten years SRC was diagnosed in 8 patients (all 8 with histologic data). The first 5 cases were treated with steroids, anti-hypertensive-cocktail and PI: all 5 died, 2 within 48 hours, 3 after 10, 15 and 300 days respectively. Three other patients were treated with ACE-inhibitors, PI and PE: all 3 died after 1, 9 and 12 months of HD. Clinical-histologic correlations showed a strong relationship between the extent of glomerular involvement and the degree of renal failure while arterial lesions seems to be more related to the past history of PSS, independently of the previous existence of hypertension. We conclude that 'true' SRC diagnosed by restrictive criteria is still a rare life-threatening syndrome and, unfortunately, no clear predictive biochemical or clinical signs can be identified; vascular renal involvement correlates to the duration of PSS independently of previous clinical evidence of renal failure or hypertension; a glomerular pattern similar to that reported for HUS/TTP syndrome is directly related to the degree of acute renal involvement; SRc may occur even in the absence of hypertension, mainly if cardiomyopathy is present; in our experience, ACE-inhibitors and plasma therapies have changed the short-time prognosis of SRC, but they may be unable to provide recovery from dialysis and do not avoid further evolution of extrarenal SPP exiting in late death.

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ACCESSION NUMBER: 1996273742 EMBASE
TITLE: Scleroderma renal crisis is still a life-threatening syndrome.
AUTHOR: Stratta P.; Besso L.; Ferrero S.; Canavese C.; Hollo S.; Ottone S.; Sandri L.; Thea A.; Mazzucco G.
CORPORATE SOURCE: Dr. P. Stratta, Department of Neprology, S. Giovanni-Molinette Hospital, C.so Dogliotti 14, 10126 Torino, Italy
SOURCE: Renal Failure, (1996) Vol. 18, No. 4, pp. 567-574.
Refs: 20
ISSN: 0886-022X CODEN: REFAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 028 Urology and Nephrology
031 Arthritis and Rheumatism
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 1996
Last Updated on STN: 1 Oct 1996

AB Scleroderma renal crisis (SRC) was known as a rare and catastrophic syndrome responsible for acute renal failure (ARF) in a context of widespread microvascular disease occurring in progressive systemic sclerosis (PSS). Following pathogenetic hypoteses, angiotensin converting enzyme (ACE) inhibitors, plasma infusions (PI), and plasma-exchange (PE) have been employed in SRC with favorable results. Our purpose was to verify whether these therapies have consistently changed the fatal prognosis of SRC, even in our experience. In the last 10 years, SRC was diagnosed in eight patients (all eight with histologic data). The first five cases were treated with steroids, antihypertensive-cocktail, and PI: all five died, two within 48 hours, three after 10, 15, and 300 days, respectively. Three other patients were treated with ACE inhibitors, PI, and PE: all three died after 1, 9, and 12 months of HD. Clinicalhistologieal correlations showed a strong relationship between the extent of glomerular involvement and the degree of renal failure, while arterial lesions seem

to be more related to the past history of PSS, independently from the previous existence of hypertension. We conclude that 'true' SRC diagnosed by restrictive criteria is still a rare life-threatening syndrome, and, unfortunately, no clear predictive biochemical or clinical signs could be identified; vascular renal involvement correlates to the duration of PSS independently of previous clinical evidence of renal failure or hypertension; a glomerular pattern similar to that reported for hemolytic-uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) syndrome is directly related to the degree of acute renal involvement; SRC may occur even in the absence of hypertension, mainly if cardiomyopathy is present; in our experience, ACE inhibitors and plasma therapies have changed the short-time prognosis of SRC, but they may be unable to provide recovery from dialysis and do not avoid further evolution of extrarenal PSS exiting in late death.

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ACCESSION NUMBER: 1994208231 EMBASE
TITLE: Renal involvement in systemic sclerosis.
AUTHOR: Steen V.D.
CORPORATE SOURCE: Dr. V.D. Steen, Rheumatology/Clinical Immunol. Div., 985 Scaife Hall, Pittsburgh Univ. School of Medicine, Pittsburgh, PA 15261, United States
SOURCE: Clinics in Dermatology, (1994) Vol. 12, No. 2, pp. 253-258. ISSN: 0738-081X CODEN: CLDEEU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jul 1994
Last Updated on STN: 27 Jul 1994

AB Renal crisis occurs in systemic sclerosis patients with rapidly progressive diffuse cutaneous thickening early in their disease course. SRC is characterized by malignant hypertension, hyperreninemia, azotemia, and microangiopathic hemolytic anemia. This complication was almost uniformly fatal but can now be treated successfully in most cases with ACE inhibitors. The result has been improved survival, reduced requirement for dialysis, and even discontinuation of dialysis after 6 to 18 months of treatment. Prompt diagnosis and early aggressive treatment of SRC with ACE inhibitors will result in the most optimal outcome.

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ACCESSION NUMBER: 2004:204105 BIOSIS
DOCUMENT NUMBER: PREV200400204648
TITLE: Targeting acute focal stroke with a novel Src kinase inhibitor: SKI - 606.
AUTHOR(S): Zaleska, M. M. [Reprint Author]; Liang, S. [Reprint Author]; Xiao, Y. [Reprint Author]; Gonzales, C. [Reprint Author]; Dilks, D. [Reprint Author]; Ye, F.; Boschelli, D.; Boschelli, F.; Pong, K. [Reprint Author]
CORPORATE SOURCE: Neurosci., Wyeth Res., Princeton, NJ, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 741.14. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003.

Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Vascular endothelial growth factor (VEGF), an angiogenic factor highly upregulated in response to ischemic injury, promotes vascular permeability (VP) and a breakdown of blood brain barrier leading to development of vasogenic edema, a major clinical complication in stroke and brain trauma patients. Recent experimental evidence implicates Src kinase in the regulation of VEGF-mediated VP in the brain following ischemic stroke. Here we report on the assessment of a potent Src kinase inhibitor SKI-606 (Golas et al., Cancer Res. 2003, 63:375) for neuroprotective efficacy in rat model of transient focal ischemia. Wistar rats were subjected to a 90 min occlusion of the middle cerebral artery (tMCAO) using an intraluminal suture approach. Following the reperfusion, animals were evaluated over the period of 48 hours for neurological function deficits, weight loss/gain and the volume of infarcted brain tissue. When administered intraperitoneally at doses of 5 or 45 mg/kg, at 85 min post induction of ischemia, SKI-606 significantly improved neurological deficits and reduced infarct volume. Treatment with a comparator, PP1, at 5 mg/kg i.p., resulted in a similar improvement in motor function. Intravenous administration of SKI-606 as a single bolus of 3, 10 or 30 mg/kg, at 30 min post-MCAO, resulted in a significant reduction in infarct volume (up to 57%) and a significant protection from neurological deficits and post-stroke weight loss. No adverse effects on blood pressure, heart rate or body temperature were observed at these doses. These data demonstrate that SKI-606 provides an effective treatment against CNS injury induced by a transient focal ischemia.

L5 ANSWER 45 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:134131 BIOSIS
DOCUMENT NUMBER: PREV200400132204
TITLE: The pituitary hormone, prolactin stimulates normal cholangiocyte proliferation by a Ca2+ and PKC mediated mechanism.
AUTHOR(S): Taffetani, Silivia [Reprint Author]; Francis, Heather [Reprint Author]; Glaser, Shannon [Reprint Author]; Phinizy, Jo Lynne [Reprint Author]; Marucci, Luca; Benedetti, Antonio; Baumann, Brandy; Reichenbach, Ramona; Venter, Julie; Alpini, Gianfranco
CORPORATE SOURCE: Scott and White Hospital, Temple, TX, USA
SOURCE: Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 684A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004

AB Cholangiocytes are the target cells of cholangiopathies, which are characterized by increases in serum levels of a number of hormones including estrogens, growth hormone and prolactin (PRL). In cholangiopathies, bile ducts proliferate or are lost. In particular, hyperprolactinemia seems to be an important event in patients with liver

cirrhosis and portal hypertension associated with a history of alcohol abuse and in patients with encephalopathy. PRL is a pituitary peptide hormone that is under the tonic inhibitory control of dopamine. In many cell types, PRL promotes cellular proliferation, differentiation, and also survival pathways by interacting with its receptor that belongs to the class I superfamily of cytokine receptors. It has been shown that PRL intracellular signaling involves different pathways such as the Ras/c-Raf/ERK cascade, the JNK/STAT, PI3K/AKT survival pathway and the Src/Ca2+/PKC-beta2 signaling pathway. There is growing information regarding cholangiocyte proliferation. Gastrointestinal hormones (e.g., gastrin and somatostatin), neuropeptides and bile salts have been shown to regulate cholangiocyte proliferation. Cholangiocyte proliferation is associated with enhanced intracellular cAMP levels, which induces an increase in intrahepatic ductal mass. Furthermore, cross-talk between intracellular Ca2+/PKC-beta2 and adenylyl cyclase regulates cholangiocyte proliferation. No information exists regarding the role of PRL in the regulation of cholangiocyte proliferation. We posed the following questions: (i) Do cholangiocytes express the PRL-receptor? (ii) Does PRL "in vivo" administration to normal rats increase cholangiocyte proliferation? and (iii) Are PRL effect on cholangiocyte proliferation mediated by a Ca2+/PKC-beta2 pathway? Methods: We first evaluated the expression of PRL receptors in liver sections (by immunohistochemistry) and purified cholangiocytes (by immunoblots) from normal female rats. Normal female rats were treated by daily IP injections of saline or ovine-prolactin (420 mug/rat, twice at day) for 1 week. Cholangiocyte proliferation was assessed in liver sections by measurement of: (i) the number of PCNA- and gamma-GT-positive cholangiocytes in liver sections; and (ii) PCNA protein expression and cAMP levels (a major determinant of cholangiocyte proliferation) in cholangiocytes isolated from the two groups of animals. To demonstrate the specificity of the PRL effects and to evaluate the mechanisms by which PRL stimulates cholangiocyte proliferation, pure cholangiocytes from normal female rats were stimulated at 37degreeC for 4 hours with PRL (100 nM) in the absence or presence of BAPTA/AM (an intracellular Ca2+ chelator, 5 muM) or Go6976 (a PKC inhibitor, 1 muM). Subsequently, we measured PCNA protein expression. Finally, we evaluate the in vitro effect of PRL on the phosphorylation of PKC-beta2, which regulates cholangiocyte proliferation. Results: Cholangiocytes express PRL receptors. Administration of PRL to normal rats determined an increase in cholangiocyte proliferation as evidenced by: (i) the increased number of PCNA- and gamma-GT-positive cholangiocytes in liver sections; and (ii) enhanced PCNA protein expression and cAMP levels in cholangiocytes. In vitro, PRL stimulated PCNA protein expression of normal female cholangiocytes, an increase that was blocked by BAPTA/AM and Go9676. Summary/conclusion: Cholangiocytes express PRL receptors. Both in vivo and in vitro, PRL increased cholangiocyte proliferation by a Ca2+/PKC-mediated mechanism associated with phosphorylation of PKC-beta2. These data suggest that in chronic liver diseases associated with hyperprolactinemia the elevated levels of prolactin may contribute to hepatic failure by adding cholestasis to the primary hepatopathy.

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ACCESSION NUMBER:	2003:329230 BIOSIS
DOCUMENT NUMBER:	PREV200300329230
TITLE:	Synergistic effect of urotensin II with serotonin on vascular smooth muscle cell proliferation.
AUTHOR(S):	Watanabe, Takuya [Reprint Author]; Katagiri, Takashi; Pakala, Rajbabu; Benedict, Claude R.
CORPORATE SOURCE:	Third Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan
SOURCE:	American Journal of Hypertension, (May 2003) Vol.

16, No. 5 Part 2, pp. 170A-171A. print.
Meeting Info.: Eighteenth Annual Scientific Meeting of the American Society of Hypertension. New York, NY, USA. May 14-17, 2003. American Society of Hypertension.
CODEN: AJHYE6. ISSN: 0895-7061.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 2003
Last Updated on STN: 22 Aug 2003

L5 ANSWER 47 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:80151 BIOSIS
DOCUMENT NUMBER: PREV200300080151
TITLE: High intraluminal pressure and cyclic stretch activate ERK1/2 via distinct pathways in the rabbit aorta in organ culture.
AUTHOR(S): Lehoux, Stephanie [Reprint Author]; Esposito, Bruno [Reprint Author]; Tedgui, Alain [Reprint Author]
CORPORATE SOURCE: INSERM U541, Paris, France
SOURCE: Circulation, (November 5 2002) Vol. 106, No. 19 Supplement, pp. II-117. print.
Meeting Info.: Abstracts from Scientific Sessions. Chicago, IL, USA. November 17-20, 2002. American Heart Association.
ISSN: 0009-7322 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003

L5 ANSWER 48 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:299228 BIOSIS
DOCUMENT NUMBER: PREV200200299228
TITLE: Patient characteristics and outcomes in a cohort of biopsy proven cases of scleroderma renal crisis(SRC).
AUTHOR(S): Kingdon, Edward J. [Reprint author]; Black, Carol M.; Stratton, Richard; Bunn, Christopher; Powis, Stephen H.; Davenport, Andrew [Reprint author]; Sweny, Paul [Reprint author]; Burns, Aine [Reprint author]
CORPORATE SOURCE: Centre for Nephrology, RFUCMS, London, UK
SOURCE: Journal of the American Society of Nephrology, (September, 2001) Vol. 12, No. Program and Abstract Issue, pp. 172A. print.
Meeting Info.: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology. San Francisco, CA, USA. October 10-17, 2001. American Society of Nephrology; International Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 May 2002
Last Updated on STN: 22 May 2002

L5 ANSWER 49 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:224527 BIOSIS

DOCUMENT NUMBER: PREV200200224527
TITLE: Scleroderma renal crisis (SRC) with severe renal failure (RF): A retrospective series of 18 patients.
AUTHOR(S): Pauti, Marie-Dominique [Reprint author]; Boulmerka, Hocine [Reprint author]; Gauthier, Eric [Reprint author]; Emmerich, Joseph; Bariety, Jean [Reprint author]; Jacquot, Christian [Reprint author]
CORPORATE SOURCE: Dept. Nephrologie, Hopital Broussais, Paris, France
SOURCE: Journal of the American Society of Nephrology, (September, 2000) Vol. 11, No. Program and Abstract Issue, pp. 161A. print.
Meeting Info.: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week. Toronto, Ontario, Canada. October 10-16, 2000. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

L5 ANSWER 50 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:275462 BIOSIS
DOCUMENT NUMBER: PREV200100275462
TITLE: alpha2 adrenergic receptors mediate contraction in rat aorta through a Src-independent pathway containing PLC, PKC, and PI3K.
AUTHOR(S): Carter, Rebecca W. [Reprint author]; Kanagy, Nancy L. [Reprint author]
CORPORATE SOURCE: University of New Mexico Health Sciences Center, 915 Camino de Salud, Albuquerque, NM, 87131-5218, USA
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A456. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jun 2001
Last Updated on STN: 19 Feb 2002

AB We previously reported that G protein coupled alpha2-AR contraction is abolished by tyrosine kinase inhibition. Other G protein coupled receptors (i.e. AT1R and 5-HTR) mediate contraction through src tyrosine kinases. We therefore hypothesized that alpha2-AR mediate contraction through a src-dependent pathway including PLC, PKC, and PI3K and that upregulation of these pathways contributes to increased alpha2-AR vascular contraction in rats made hypertensive with chronic nitric oxide synthase inhibition (NOS-I). Contractile studies in endothelium-denuded thoracic aortae rings were performed to determine the contribution of each proposed signaling molecule to alpha2-AR contraction. Data were compared using two-way ANOVA and differences considered significant at $p<0.05$. The src kinase inhibitor PP1 (10muM) did not effect UK14,304 (3muM) contraction, although the same concentration of PP1 attenuated serotonin (10muM) contraction by 40+-5% in control and 22+-6% in NOS-I rings. The PLC inhibitor U73122 (10muM) attenuated UK14,304 contraction (58+-3% in both control and NOS-I rings). Two PKC inhibitors also reduced contraction.

Calphostin C was more effective in control rings (0.5muM, 59+-4% in control, 34+-7% in NOS-I rings), while chelerythrin chloride was equally effective in both (10muM, 66+-12% in control, 61+-10% in NOS-I rings). The PI3K inhibitor LY294002 (10muM) attenuated UK14,304 contraction (39+-13% in control, 53+-10% in NOS-I rings). Only the PKC inhibitor calphostin C differentially affected rings from control and NOS-I treated rats. However, PKC inhibition by chelerythrin was not different between groups. Immunoblots of aortic tissues stimulated with UK14,304 (3muM) revealed phosphorylated PLCgamma and PI3K. These data indicate that alpha2-AR mediate contraction through a tyrosine kinase-dependent but src-independent pathway that includes PLC, PKC, and PI3K. Furthermore, increased alpha2-AR sensitivity associated with NOS-I is not due to differential contribution of the signaling molecules studied, although differences may exist in PKC isoform activation.

L5 ANSWER 51 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:105849 BIOSIS
DOCUMENT NUMBER: PREV200100105849
TITLE: Increased generation of vascular reactive oxygen species by Ang II is mediated via Src-dependent pathways in essential hypertension.
AUTHOR(S): Touyz, Rhian M. [Reprint author]; Schiffrin, Ernesto L. [Reprint author]
CORPORATE SOURCE: Clin Research Inst of Montreal, Montreal, PQ, Canada
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.302. print.
Meeting Info.: Abstracts from American Heart Association Scientific Sessions 2000. New Orleans, Louisiana, USA. November 12-15, 2000. American Heart Association.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

L5 ANSWER 52 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:95124 BIOSIS
DOCUMENT NUMBER: PREV200100095124
TITLE: Mechanisms of c-fos expression in response to mechanical stimulation in intact small arteries.
AUTHOR(S): Wesselman, J. P. [Reprint author]; De Mey, J. G. [Reprint author]; Dobrian, A. D.; Schriver, S. D.; Prewitt, R. L.
CORPORATE SOURCE: Pharmacology and Toxicology, University Maastricht, Maastricht, Netherlands
SOURCE: Journal of Submicroscopic Cytology and Pathology, (July, 2000) Vol. 32, No. 3, pp. 424. print.
Meeting Info.: XIth International Vascular Biology Meeting. Geneva, Switzerland. September 05-09, 2000.
ISSN: 1122-9497.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2001
Last Updated on STN: 15 Feb 2002

L5 ANSWER 53 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:22508 BIOSIS

DOCUMENT NUMBER: PREV200100022508
TITLE: Src-dependent ERK1/2-mediated signaling pathways and associated Ang II-stimulated growth responses are altered in vascular smooth muscle cells from hypertensive patients.
AUTHOR(S): Wu, X.-H. [Reprint author]; Touyz, R. M. [Reprint author]; He, G. [Reprint author]; Park, J. B. [Reprint author]; El Mabrouk, M. [Reprint author]; Schiffrin, E. L. [Reprint author]
CORPORATE SOURCE: Montreal, PQ, Canada
SOURCE: Canadian Journal of Cardiology, (September, 2000) Vol. 16, No. Supplement F, pp. 153F. print.
Meeting Info.: 53rd Annual Meeting of the Canadian Cardiovascular Society. Vancouver, British Columbia, Canada. October 20-November 01, 2000. Canadian Cardiovascular Society.
CODEN: CJCAEX. ISSN: 0828-282X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jan 2001
Last Updated on STN: 12 Feb 2002

L5 ANSWER 54 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:155621 BIOSIS
DOCUMENT NUMBER: PREV200000155621
TITLE: Clinicopathologic prognostic factors in scleroderma renal crisis (SRC).
AUTHOR(S): Shafer, A. [Reprint author]; Medsger, T. [Reprint author]; Johnson, J. P. [Reprint author]; Borochovitz, D.; Bastacky, S. [Reprint author]
CORPORATE SOURCE: University of Pittsburgh Medical Center, Pittsburgh, PA, USA
SOURCE: Laboratory Investigation, (Jan., 2000) Vol. 80, No. 1, pp. 178A. print.
Meeting Info.: 2000 Annual Meeting United States and Canadian Academy of Pathology. New Orleans, Louisiana, USA. March 25-31, 2000.
CODEN: LAINAW. ISSN: 0023-6837.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Apr 2000
Last Updated on STN: 4 Jan 2002

L5 ANSWER 55 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:94653 BIOSIS
DOCUMENT NUMBER: PREV199900094653
TITLE: Angiotensin II signal transduction in vascular smooth muscle: Pathways activated by specific tyrosine kinases.
AUTHOR(S): Berk, Bradford C. [Reprint author]
CORPORATE SOURCE: Cardiol. Unit, Box 679, Univ. Rochester Med. Cent., 601 Elmwood Ave., Rochester, NY 14642, USA
SOURCE: Journal of the American Society of Nephrology, (Jan., 1999) Vol. 10, No. SUPPL. 11, pp. S62-S68. print.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Mar 1999

Last Updated on STN: 1 Mar 1999

AB In this review, the signal events regulated by angiotensin II (AngII) in vascular smooth muscle are analyzed based on activation of specific tyrosine kinases. AngII has been shown to play a critical role in the pathogenesis of hypertension, inflammation, atherosclerosis, and congestive heart failure. The expanding role of AngII indicates that multiple signal transduction pathways are likely to be activated in a tissue-specific manner. Although at least three AngII receptors have been characterized, it seems that the AngII type I receptor (AT1R) is physiologically most important since pharmacologic inhibitors of the AT1R block most AngII signal events and have beneficial effects on cardiovascular disease. The AT1R is a seven transmembrane-spanning G protein-coupled receptor that regulates intracellular signal events by activation of Gq and Gi. However, many recent data indicate that activation of tyrosine kinases by several different mechanisms contributes to AngII effects in target tissues. Tyrosine kinases activated by AngII include c-Src, focal adhesion kinase (FAK), Pyk2 (CADTK), Janus kinases (JAK2 and TYK2), and the receptor tyrosine kinases Axl, epidermal growth factor, and platelet-derived growth factor. Finally, unknown tyrosine kinases may mediate tyrosine phosphorylation of paxillin, Shc, Raf, and phospholipase C-gamma after AngII stimulation. These AngII-regulated tyrosine kinases seem to be required for AngII effects such as vasoconstriction, proto-oncogene expression, and protein synthesis based on studies with tyrosine kinase inhibitors. Thus, understanding An-II-stimulated signaling events, especially those related to tyrosine kinase activity, may form the basis for the development of new therapies for cardiovascular diseases.

L5 ANSWER 56 OF 66 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:22815 BIOSIS
DOCUMENT NUMBER: PREV199800022815
TITLE: Outcome of scleroderma renal crisis (SRC).
AUTHOR(S): Steen, Virginia D. [Reprint author]
CORPORATE SOURCE: Georgetown Univ., Washington, DC, USA
SOURCE: Journal of the American Society of Nephrology, (Sept., 1997) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 149A. print.
Meeting Info.: 30th Annual Meeting of the American Society of Nephrology. San Antonio, Texas, USA. November 2-5, 1997. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jan 1998
Last Updated on STN: 5 Jan 1998

L5 ANSWER 57 OF 66 MEDLINE on STN

ACCESSION NUMBER: 2002150173 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11882598
TITLE: Src autophosphorylation is an early event in pressure-mediated signaling pathways in isolated resistance arteries.
AUTHOR: Rice Darian C; Dobrian Anca D; Schriver Suzanne D; Prewitt Russell L
CORPORATE SOURCE: Department of Physiological Sciences, Eastern Virginia Medical School, Norfolk, VA 23507, USA.
SOURCE: Hypertension, (2002 Feb) Vol. 39, No. 2 Pt 2, pp. 502-7.
Journal code: 7906255. E-ISSN: 1524-4563.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 8 Mar 2002
Last Updated on STN: 3 Apr 2002
Entered Medline: 28 Mar 2002

AB Elevated blood pressure is associated with varying degrees of arterial growth and remodeling. The mechanisms by which mechanical stress is converted into cellular alteration have yet to be fully elucidated. Our laboratory has demonstrated that Src tyrosine kinases and the extracellular signal-regulated kinase subtype of the mitogen-activated protein kinase family mediate pressure-induced c-fos expression in rat mesenteric arteries. Others have reported involvement of integrin and growth factor receptor signaling pathways. Our goal was to determine the role of Src, focal adhesion kinase (FAK), and platelet-derived growth factor (PDGF) receptor signaling in the upstream initiation of these events. Pairs of rat mesenteric arteries were pressurized to 90 mm Hg (control), and then one was raised to 140 mm Hg for 1, 3, or 5 minutes. Western blotting revealed that Src -pY(418) was elevated 2.4-fold over control values at 1 minute and 2.8-fold at 3 minutes and returned to control at 5 minutes. Significant FAK-Y(397) phosphorylation was observed only after 3 and 5 minutes of pressure stimulus and was blocked entirely by Src inhibition. Src-pY(215) activity (associated with PDGF receptor activation) does not seem to be involved at any of the time points tested. These data demonstrate that Src-Y(418) autophosphorylation is an early event in pressure mechanotransduction and leads to activation of FAK-Y(397). This finding suggests that Src may be the messenger that initiates and propagates the cellular growth response to pressure stimulus, and FAK is one of its downstream targets. Src phosphorylation due to PDGF receptor activation does not seem to be involved in the initial response.

L5 ANSWER 58 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2001500552 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11549343
TITLE: Src and multiple MAP kinase activation in cardiac hypertrophy and congestive heart failure under chronic pressure-overload: comparison with acute mechanical stretch.
AUTHOR: Takeishi Y; Huang Q; Abe J; Glassman M; Che W; Lee J D; Kawakatsu H; Lawrence E G; Hoit B D; Berk B C; Walsh R A
CORPORATE SOURCE: Department of Medicine, Case Western Reserve University, Cleveland, OH, 44106-5029, USA.
CONTRACT NUMBER: HL44721 (United States NHLBI)
HL49192 (United States NHLBI)
HL52318 (United States NHLBI)
SOURCE: Journal of molecular and cellular cardiology, (2001 Sep) Vol. 33, No. 9, pp. 1637-48.
Journal code: 0262322. ISSN: 0022-2828.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 11 Sep 2001

Last Updated on STN: 25 Jan 2002
Entered Medline: 3 Jan 2002

AB Activation of members of the mitogen-activated protein (MAP) kinase family and their downstream effectors has been proposed to play a key role in the pathogenesis of cell survival, ischaemic preconditioning, cardiac hypertrophy and heart failure. This study investigated the responses of Src kinase and multiple MAP kinases during the transition from compensated pressure-overload hypertrophy to decompensated congestive heart failure. Extracellular signal-regulated protein kinase (ERK) 1/2, p38, and Src were activated by chronic pressure-overload and their activity was sustained for 8 weeks after aortic banding. In contrast, while p90 ribosomal S6 kinase (90RSK) and big MAP kinase 1 (BMK1) were activated in compensated hypertrophy, their activities were significantly decreased in hearts with heart failure. No changes were found in C-Jun NH2 terminal kinase (JNK) activity after aortic banding. These data suggest that differential activation of MAP kinase family members may contribute to the transition from compensated to decompensated hypertrophy. We also examined acute effects of mechanical stretch on the activation of these kinases in normal and hypertrophied hearts. In the isolated coronary-perfused heart, a balloon in the left ventricle was inflated to achieve minimum end-diastolic pressure of 25 mmHg for 10-20 min. In normal guinea pig hearts, stretch activated ERK1/2, p90RSK, p38, Src, and BMK1 but not JNK. However in hypertrophied hearts, further activation of these kinases was not observed by acute mechanical stretch. Mechanical stretch-induced activation of ERK1/2 and p38 kinase in normal hearts was attenuated significantly by a protein kinase C inhibitor, chelerythrine. We demonstrate that ERK1/2, p90RSK, p38, Src, and BMK1 are activated by chronic pressure-overload and by acute mechanical stretch. These data suggest that Src, BMK1 and p90RSK play a role as novel signal transduction pathways leading to cardiac hypertrophy. In addition, the differential inhibition of p90RSK and BMK1 in hearts with congestive heart failure suggests the specific role of these two kinases to maintain cardiac function under chronic pressure-overload.

L5 ANSWER 59 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2001257030 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11210764
TITLE: Scleroderma renal crisis (SRC): hypertensive, normotensive.
AUTHOR: Endo H
CORPORATE SOURCE: Kitasato University School of Medicine, Department of Internal Medicine.
SOURCE: Nihon Rinsho Men'eki Gakkai kaishi = Japanese journal of clinical immunology, (2000 Dec) Vol. 23, No. 6, pp. 656-60.
Journal code: 9505992. ISSN: 0911-4300.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 21 May 2001
Last Updated on STN: 21 May 2001
Entered Medline: 17 May 2001

L5 ANSWER 60 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2001099781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11121380
TITLE: A role for PYK2 in regulation of ERK1/2 MAP kinases and PI

3-kinase by ANG II in vascular smooth muscle.
AUTHOR: Rocic P; Govindarajan G; Sabri A; Lucchesi P A
CORPORATE SOURCE: Department of Physiology and Biophysics, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.
CONTRACT NUMBER: HL-56046 (United States NHLBI)
SOURCE: American journal of physiology. Cell physiology, (2001 Jan) Vol. 280, No. 1, pp. C90-9.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 19 Dec 2002
Entered Medline: 1 Feb 2001

AB Abnormal vascular smooth muscle cell (VSMC) growth plays a key role in the pathogenesis of hypertension and atherosclerosis. Angiotensin II (ANG II) elicits a hypertrophic growth response characterized by an increase in protein synthesis without cell proliferation. The present study investigated the role of the nonreceptor tyrosine kinase PYK2 in the regulation of ANG II-induced signaling pathways that mediate VSMC growth. Using coimmunoprecipitation analysis, the role of PYK2 as an upstream regulator of both extracellular signal-related kinase (ERK) 1/2 mitogen-activated protein kinase and phosphatidylinositol 3-kinase (PI 3-kinase) pathways was examined in cultured rat aortic VSMC. ANG II (100 nM) promoted the formation of a complex between PYK2 and the ERK1/2 regulators Shc and Grb2. ANG II caused a rapid and Ca(2+)-dependent tyrosine phosphorylation of the adapter molecule p130Cas, which coimmunoprecipitated both PYK2 and PI 3-kinase in ANG II-treated VSMC. Complex formation between PI 3-kinase and p130Cas and PYK2 was associated with a rapid phosphorylation of the ribosomal p70(S6) kinase in a Ca(2+)- and tyrosine kinase-dependent manner. These data suggest that PYK2 is an important regulator of multiple signaling pathways involved in ANG II-induced VSMC growth.

L5 ANSWER 61 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2001041436 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11073839
TITLE: Pulsatile stretch-induced extracellular signal-regulated kinase 1/2 activation in organ culture of rabbit aorta involves reactive oxygen species.
AUTHOR: Lehoux S; Esposito B; Merval R; Loufrani L; Tedgui A
CORPORATE SOURCE: INSERM U541 and IFR "Circulation," Hopital Lariboisiere, Paris, France.
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2000 Nov) Vol. 20, No. 11, pp. 2366-72.
Journal code: 9505803. E-ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 21 May 2001
Entered Medline: 7 Dec 2000

AB Increased steady intraluminal pressure in blood vessels activates the extracellular signal-regulated kinase (ERK)1/2 pathway. However, signal transduction of pulsatile stretch has not been elucidated. Using an organ

culture model of rabbit aorta, we studied ERK1/2 activation by pulsatility in vessels maintained at 80 mm Hg for 24 hours. ERK1/2 activity was evaluated by in-gel kinase assays and by Western blot. Compared with control aortas without pulsatility, aortas submitted to a pulsatile 10% variation in vessel diameter displayed a significant increase in ERK1/2 activity (207+/-12%, P<0.001), which remained high after removal of the endothelium. Unlike steady overstretch, pulsatile stretch-induced activation of ERK1/2 was not modified by herbimycin A, a Src family tyrosine kinase inhibitor, but was reduced by other tyrosine kinase inhibitors, tyrphostin A48 and genistein (162+/-27% and 144+/-14%, respectively). Conversely, ERK1/2 activity was markedly decreased in pulsatile vessels treated with staurosporine (114+/-18%) although neither of the more specific protein kinase C inhibitors, Ro-31-8220 or Go-6976, blocked ERK1/2 activation (209+/-24% and 238+/-34%, respectively), whereas staurosporine had no effect on steady overstretch-induced ERK1/2 activation. Pulsatility induced superoxide anion generation, which was prevented by the NADPH oxidase inhibitor diphenyleneiodonium. Furthermore, polyethylene glycol-superoxide dismutase completely abolished ERK1/2 activation by pulsatility (114+/-12%). Finally, ERK1/2 and O(2)(-) levels in freshly isolated vessels were equivalent to the levels found in pulsatile vessels. In conclusion, pulsatile stretch activates ERK1/2 in the arterial wall via pathways different from those induced by steady overstretch. Pulsatility might be considered a physiological stimulus that maintains a certain degree of ERK1/2 activation via oxygen-derived free radical production.

L5 ANSWER 62 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2000421641 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10916078
TITLE: Angiotensin II-induced growth of vascular smooth muscle cells requires an Src-dependent activation of the epidermal growth factor receptor.
AUTHOR: Bokemeyer D; Schmitz U; Kramer H J
CORPORATE SOURCE: Department of Medicine Medizinische Poliklinik, and Division of Nephrology, University of Bonn, Germany.. bokemeyer@uni-bonn.de
SOURCE: Kidney international, (2000 Aug) Vol. 58, No. 2, pp. 549-58.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 15 Sep 2000
Last Updated on STN: 15 Sep 2000
Entered Medline: 7 Sep 2000

AB BACKGROUND: Angiotensin II (Ang II) is a potent stimulus of vascular smooth muscle cell (VSMC) growth. Activation of extracellular signal-regulated kinase (ERK), the archetypal mitogen-activated protein (MAP) kinase, and phosphatidylinositol 3 (PI3) kinase are critical steps in Ang II-induced mitogenic signaling. However, the mechanism involved in the activation of these kinases upon binding of Ang II to its receptor is poorly understood. METHODS: In the present study, we examined the role of the epidermal growth factor receptor (EGFR) in Ang II signaling in VSMCs employing immunoprecipitation, Western blot analysis, kinase immunocomplex assay, and [3H]-thymidine incorporation. RESULTS: A time-dependent tyrosine phosphorylation of the EGFR in response to Ang II was observed that was mediated by the Ang II type 1 receptor. This transactivation of the EGFR was blocked in the presence of PP1, an inhibitor of the

intracellular Src-like tyrosine kinases. The tyrphostin AG 1478, a selective EGFR antagonist, inhibited both Ang II- and EGF-induced tyrosine phosphorylation of the EGFR. Furthermore, Ang II induced the binding of the adaptor protein Shc to the EGFR, leading to phosphorylation of Shc. In addition, the same nanomolar concentrations of AG 1478 that were effective in EGF signaling blocked the Ang II-induced activation of ERK and PI3 kinase in a dose-dependent manner. Proliferation of VSMCs, detected by measurements of DNA synthesis, following stimulation with Ang II was potently inhibited in the presence of AG 1478 or PP1. CONCLUSION: Our data suggest that EGFR serves as a role in mitogenic signaling following stimulation with Ang I through a ligand-independent and Src-dependent transactivation of the EGFR. Furthermore, we demonstrate this transactivation as a pivotal step in Ang II-induced activation of MAP kinase and PI3 kinase, as well as growth of VSMCs.

L5 ANSWER 63 OF 66 MEDLINE on STN
ACCESSION NUMBER: 2000212626 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10750588
TITLE: Role of the renin-angiotensin system in cardiac hypertrophy.
AUTHOR: Yamazaki T; Komuro I; Yazaki Y
CORPORATE SOURCE: Department of Cardiovascular Medicine, Graduate School of Medicine, University of Tokyo, Japan.
SOURCE: The American journal of cardiology, (1999 Jun 17) Vol. 83, No. 12A, pp. 53H-57H. Ref: 29
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 27 Apr 2000
Last Updated on STN: 13 Mar 2003
Entered Medline: 19 Apr 2000

AB Hypertrophy is an adaptive response of the heart to hemodynamic overload such as hypertension. However, it is generally accepted that cardiac hypertrophy is one of the most critical risk factors of heart disease. Therefore, for the treatment of hypertension it is important to understand the mechanism of cardiac hypertrophy and to establish effective pharmaceutical interventions. Mechanical stretch induced by hypertension is an initial factor leading to cardiac hypertrophy. In an in vivo study using spontaneously hypertensive rats, an angiotensin II type 1 receptor antagonist, TCV116, decreased left ventricular weight, left ventricular wall thickness, transverse myocyte diameter, relative amount of V3 myosin heavy chain, and interstitial fibrosis, whereas treatment with hydrolazine did not. In an in vitro study using cultured cardiomyocytes of neonatal rats, mechanical stretch activated second messengers, such as extracellular signal-regulated protein kinase (ERK), followed by increased protein synthesis. Additionally, in the stretch-conditioned medium, the levels of angiotensin II and endothelin-1 concentrations were increased. Moreover, the Na+/H+ exchanger activated by mechanical stretch modulated the hypertrophic responses of cardiomyocytes. To further elucidate whether angiotensin II is indispensable for mechanical stress-induced cardiac hypertrophy, mechanical stretch-induced ERK activation was examined in angiotensin II type 1a receptor knock-out mice. Although the addition of angiotensin II had no effects on the ERK activity in cardiomyocytes of angiotensin II type 1a receptor knockout mice, mechanical stretch induced a larger increase in the ERK activity in cardiac myocytes from these mice compared with cardiac myocytes of wild-type mice. These results suggest that mechanical stretch could induce hypertrophic responses in cardiac myocytes

even in the absence of angiotensin II. The pathways leading to ERK activation differed between cell types. In cardiac fibroblasts, angiotensin II activated ERK via the G(beta)gamma subunit of Gi, Src, Shc, Grb2, and Ras, whereas Gq and protein kinase C were critical in cardiomyocytes.

L5 ANSWER 64 OF 66 MEDLINE on STN
ACCESSION NUMBER: 1999174538 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10076920
TITLE: Role of tissue angiotensin II in myocardial remodelling induced by mechanical stress.
AUTHOR: Yamazaki T; Yazaki Y
CORPORATE SOURCE: Department of Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, Japan.
SOURCE: Journal of human hypertension, (1999 Jan) Vol. 13 Suppl 1, pp. S43-7; discussion S49-50. Ref: 32
Journal code: 8811625. ISSN: 0950-9240.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 11 May 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Apr 1999

AB In an in vivo study, spontaneously hypertensive rats (SHR) were treated with an angiotensin II (Ang II) type 1 receptor antagonist of candesartan or hydralazine. Untreated SHR progressively developed severe hypertension, and treatment with candesartan or hydralazine decreased blood pressure. Candesartan reduced left ventricular (LV) weight, LV wall thickness, transverse myocyte diameter, the relative amount of V3 myosin heavy chain, and interstitial fibrosis, while treatment with hydralazine slightly prevented an increase in LV wall thickness, but did not exert a significant reduction on other parameters. In an in vitro study, neonatal rat cardiomyocytes were cultured on deformable silicone dishes. Stretching cardiomyocytes activated second messengers such as protein kinase C, Raf-1 kinase, and mitogen-activated protein (MAP) kinase, increasing protein synthesis, enhancing endothelin (ET)-1 release, activating the Na+/H+ ion exchanger. Moreover, pretreatment with candesartan diminished an increase in phenylalanine incorporation, MAP kinase activity, and c-fos gene expression induced by the stretching of cardiomyocytes. This suggests that the cardiac renin-angiotensin system is linked to the formation of pressure-overload hypertrophy and that Ang II increases the growth of cardiomyocytes by an autocrine mechanism. Finally, we examined the signalling pathways leading to MAP kinase activation both in cardiac myocytes and in cardiac fibroblasts. Ang II-evoked signal transduction pathways differed between cell types. In cardiac fibroblasts, Ang II activated MAP kinase through a pathway including the Gbetagamma subunit of Gi protein, Src, Shc, Grb2, and Ras, while Gq and protein kinase C were important in cardiac myocytes.

L5 ANSWER 65 OF 66 MEDLINE on STN
ACCESSION NUMBER: 1998318983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9654914
TITLE: A case of scleroderma renal crisis with massive pericardial effusion and positivity on antiphospholipid antibody test.
AUTHOR: Ichikawa H; Amano T; Fukuda S; Kataoka H; Kawabata K; Nagake Y; Makino H

CORPORATE SOURCE: Department of Medicine III, Okayama University Medical School, Japan.
SOURCE: Nippon Jinzo Gakkai shi, (1998 May) Vol. 40, No. 4, pp. 295-300.
Journal code: 7505731. ISSN: 0385-2385.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (CASE REPORTS)
(ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 25 Sep 1998
Last Updated on STN: 25 Sep 1998
Entered Medline: 15 Sep 1998

AB A 47-year-old woman was admitted to our hospital for evaluation of general fatigue and dyspnea. She had been diagnosed with progressive systemic sclerosis (PSS) when she was 39 years of age, on the basis of Raynaud's phenomenon, proximal sclerosis, and pigmentation of the skin. On admission, her blood pressure was 206/128 mmHg. Funduscopy revealed grade III (Keith & Wagener) hypertensive retinopathy. Laboratory data showed positivity for anti-nuclear antibody and anticardiolipin beta 2 glycoprotein I antibody, and the plasma level of renin activity (PRA) was abnormally high. Chest X-ray and UCG revealed massive pericardial effusion. On the second hospital day, she was operated on for pericardiodiaphragmatic fenestration. The volume of pericardial effusion amounted to more than 2000 ml. Post operative malignant hypertension persisted. Laboratory data showed thrombocytopenia, hemolytic anemia, and acute renal failure. We diagnosed scleroderma renal crisis (SRC) associated with antiphospholipid syndrome. Following the initiation of angiotensin converting enzyme inhibitor (ACE-I) combined with calcium antagonist and alpha-one blocker, her blood pressure and PRA decreased. She also had been treated with aspirin 81 mg daily. These therapies were effective in recovering the platelet count and stopped the progression of anemia and renal failure. Although either the finding of large pericardial effusion or SRC is associated with poor prognosis in PSS, this case has had a good clinical course. In this case, the findings suggested that anti-phospholipid antibody may have contributed to the pericarditis and SRC.

L5 ANSWER 66 OF 66 MEDLINE on STN
ACCESSION NUMBER: 87267603 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2886046
TITLE: Special uses for captopril.
AUTHOR: Materson B J
SOURCE: American journal of kidney diseases : the official journal of the National Kidney Foundation, (1987 Jul) Vol. 10, No. 1 Suppl 1, pp. 88-93. Ref: 51
Journal code: 8110075. ISSN: 0272-6386.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198708
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 13 Aug 1987

AB Plasma renin activity (PRA) is markedly increased by captopril. There is not enough separation between the changes in PRA of patients with renal artery stenosis (RAS) to separate them reliably from those with essential

hypertension. A minimal response may suggest primary aldosteronism. Captopril does increase the ratio of PRA in the venous blood from a kidney with RAS to that of the contralateral kidney. Captopril, 25 to 50 mg orally, given before renal vein PRA sampling will increase the sensitivity and specificity of the test. Treatment with current antihypertensive drugs need not be discontinued. Scleroderma renal crisis (SRC) used to be uniformly lethal within a few months. Modern, aggressive antihypertensive therapy has made survival of 2 or more years common. Not all patients respond, and some progress to renal failure despite good BP control. Captopril has been used with success in some patients with idiopathic edema. In conclusion, captopril markedly enhances the accuracy of renal vein renin assay for the diagnosis of RAS and is of major value in the treatment of SRC.

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